IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES, INC., ET AL.,	)	
	)	C.A. No. 08-21-GMS-LPS
Plaintiffs,	)	(Consolidated)
	)	
v.	)	**PUBLIC VERSION**
	)	
COBALT LABORATORIES INC., ET AL.,	)	
	)	
Defendants.	)	

APPENDIX TO DEFENDANTS' REPLY BRIEF TO PLAINTIFFS' OPPOSITION TO DEFENDANTS' MOTION TO DISMISS FOR LACK OF PERSONAL JURISDICTION

VOLUME II OF II

EXHIBITS 11 TO 25

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Dated: July 22, 2008
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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CERTIFICATE OF SERVICE

I, David E. Moore, hereby certify that on July 29, 2008, the attached document was electronically filed with the Clerk of the Court using CM/ECF which will send notification to the registered attorney(s) of record that the document has been filed and is available for viewing and downloading.

I further certify that on July 29, 2008, the attached document was Electronically Mailed to the following person(s):

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EXHIBIT 11

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 12

THIS EXHIBIT HAS BEEN REDACTED IN ITS ENTIRETY

EXHIBIT 13

4 of 100 DOCUMENTS

THIS DATA IS FOR INFORMATIONAL PURPOSES ONLY

CERTIFICATION CAN ONLY BE OBTAINED THROUGH THE ISSUING GOVERNMENT AGENCY

NEW JERSEY DEPARTMENT OF STATE

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Business Address:
116 VILLAGE BLVD SUITE 200
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Status: ACTIVE

Filing Date: 7/9/2002

Registered Agent: CORPORATION SERVICE COMPANY

Registered Office:
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Filing Number: 100883141

EXHIBIT 14

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UNITED STATES
DISTRICT COURT

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SCHERING CORPORATION, Plaintiff, v. ZYDUS PHARMACEUTICALS, USA, INC., SANDOZ INC., MYLAN PHARMACEUTICALS INC., ORGENUS PHARMA, INC., ORCHID CHEMICALS & PHARMACEUTICALS, LTD., L. PERRIGO CO., PERRIGO CO., GLENMARK PHARMACEUTICALS INC., USA, GLENMARK PHARMACEUTICALS, LTD., GEOPHARMA, INC., BELCHER PHARMACEUTICALS, INC., LUPIN PHARMACEUTICALS INC., LUPIN LTD., RANBAXY INC., RANBAXY LABORATORIES LTD., DR. REDDY'S LABORATORIES, INC., DR. REDDY'S LABORATORIES, LTD., CARACO PHARMACEUTICAL LABORATORIES, LTD., SUN PHARMACEUTICAL INDUSTRIES LTD., WATSON PHARMACEUTICALS, INC., and WATSON LABORATORIES, INC., Defendants.	Civil Action No. _____

COMPLAINT

Plaintiff Schering Corporation ("Schering"), for its Complaint against Defendants Zydus Pharmaceuticals, USA, Inc. ("Zydus"), Sandoz Inc. ("Sandoz"), Mylan Pharmaceuticals Inc. ("Mylan"), Orgenus Pharma, Inc. ("Orgenus"), Orchid Chemicals & Pharmaceuticals Ltd. ("Orchid Ltd."), L. Perrigo Company ("L. Perrigo"), Perrigo Company ("Perrigo Co."), Glenmark Pharmaceuticals Inc., USA ("Glenmark USA"), Glenmark Pharmaceuticals, Ltd. ("Glenmark Ltd."), GeoPharma, Inc. ("GeoPharma"), Belcher Pharmaceuticals, Inc. ("Belcher"), Lupin Pharmaceuticals Inc. ("Lupin Pharmaceuticals"), Lupin Limited ("Lupin Ltd."), Ranbaxy Inc., Ranbaxy Laboratories Limited ("Ranbaxy Laboratories"), Dr. Reddy's Laboratories, Inc. ("DRLI"), Dr. Reddy's Laboratories, Ltd. ("DRLL"), Caraco Pharmaceutical Laboratories, Ltd. ("Caraco"), Sun Pharmaceutical Industries Ltd. ("Sun Ltd."), Watson Pharmaceuticals, Inc. ("Watson Pharmaceuticals"), and Watson Laboratories, Inc. ("Watson Laboratories"), (collectively, "Defendants"), hereby alleges as follows.

Parties

1.A. Plaintiff Schering is a New Jersey corporation having places of business throughout New Jersey, including a place of business at 3070 Route 22 West, Branchburg, New Jersey 08876.

1.B. Upon information and belief, Defendant Zydus is a New Jersey corporation having a place of business at 508 Carnegie Center, Princeton, New Jersey 08540.

1.C. Upon information and belief, Defendant Sandoz is a Delaware corporation having a place of business at 506 Carnegie Center, Princeton, New Jersey 08540.

1.D. Upon information and belief, Defendant Mylan is a West Virginia corporation having a place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26504. Upon information and belief, Defendant Mylan is registered to do business in New

Jersey and has appointed Corporation Service Company of West Trenton, New Jersey as its registered agent in New Jersey for the receipt of service of process.

1.E. Upon information and belief, Defendant Orgenus is a New Jersey corporation and wholly owned subsidiary, agent and alter-ego of Defendant Orchid Ltd. having a place of business at 116 Village Boulevard, Princeton, New Jersey 08540.

1.F. Upon information and belief, Defendant Orchid Ltd. is an Indian corporation having a place of business at Plot No. B3-B6 & B11-B14, Sipcot Industrial Park, Irungattukottai, Sriperumbudur (TK) - 602 105, Kancheepuram District, Tamil Nadu, India. Upon information and belief, Defendant Orchid Ltd. is registered to do business in New Jersey and has appointed Corporation Service Company of West Trenton, New Jersey as its registered agent in New Jersey for the receipt of service of process.

1.G. Upon information and belief, Defendant L. Perrigo is a Michigan corporation and wholly owned subsidiary, agent and alter-ego of Defendant Perrigo Co. having a place of business at 71 Suttons Lane, Piscataway, New Jersey 08854.

1.H. Upon information and belief, Defendant Perrigo Co. is a Michigan corporation having a place of business at 515 Eastern Avenue, Allegan, Michigan 49010. Upon information and belief, Defendant Perrigo Co. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant L. Perrigo.

1.I. Upon information and belief, Defendant Glenmark USA is a Delaware corporation and wholly owned subsidiary, agent and alter-ego of Defendant Glenmark Ltd. having a place of business at 750 Corporate Drive, Mahwah, New Jersey 07430.

1.J. Upon information and belief, Defendant Glenmark Ltd. is an Indian corporation having a place of business at Glenmark House, HDO–Corporate Building, Wing -A, B. D. Sawant Marg, Chakala, Off Western Express Highway, Andheri [East], Mumbai 400 099, India. Upon information and belief, Defendant Glenmark Ltd. has appointed Dr. Vijay Soni, Executive Vice President – IP of Defendant Glenmark USA, which is located at 750 Corporate Drive, Mahwah, New Jersey 07430, as its agent in New Jersey for the receipt of any service of process in this action.

1.K. Upon information and belief, Defendant GeoPharma is a Florida corporation having a place of business at 6950 Bryan Dairy Road, Largo, Florida 33777. Upon information and belief, Defendant GeoPharma manufactures numerous products for sale and use throughout the United States, including in this judicial district, including through its subsidiaries, agents and alter-egos.

1.L. Upon information and belief, Defendant Belcher is a Florida corporation and wholly owned subsidiary, agent and alter-ego of Defendant GeoPharma having a place of business at 6950 Bryan Dairy Road, Largo, Florida 33777.

1.M. Upon information and belief, Defendant Lupin Pharmaceuticals is a Virginia corporation and wholly owned subsidiary, agent and alter-ego of Defendant Lupin Ltd. having a place of business at Harborplace Tower, 111 South Calvert Street, Baltimore, Maryland 21202. Upon information and belief, Defendant Lupin Pharmaceuticals is registered to do business in New Jersey and has appointed National Registered Agents, Inc. of Princeton, New Jersey as its registered agent in New Jersey for the receipt of service of process.

1.N. Upon information and belief, Defendant Lupin Ltd. is an Indian corporation having a place of business at 159 CST Road, Kalina, Santacruz (E), Mumbai 400

098, India. Upon information and belief, Defendant Lupin Ltd. manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant Lupin Pharmaceuticals.

1.O. Upon information and belief, Defendant Ranbaxy Inc. is a Delaware corporation and wholly owned subsidiary, agent and alter-ego of Defendant Ranbaxy Laboratories having a place of business at 600 College Road East, Princeton, New Jersey, 08540.

1.P. Upon information and belief, Defendant Ranbaxy Laboratories is an Indian corporation having a place of business at Plot 90, Sector 32, Gurgaon -122001 (Haryana), India. Upon information and belief, Defendant Ranbaxy Laboratories manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant Ranbaxy Inc.

1.Q. Upon information and belief, Defendant DRLI is a New Jersey corporation and wholly owned subsidiary, agent and alter-ego of DRLL having a place of business at 200 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807.

1.R. Upon information and belief, Defendant DRLL is an Indian corporation having a place of business at 7-1-27 Ameerpet, Hyderabad 500 016, Andhra Pradesh, India. Upon information and belief, Defendant DRLL manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district, through its wholly owned subsidiary, agent and alter-ego Defendant DRLI. Upon information and belief, Defendant DRLL has appointed Lee Banks, Esq. of Defendant DRLI, which is located at 200 Somerset Corporate Boulevard, Bridgewater, New Jersey 08807, as its agent in New Jersey for the receipt of any service of process in this action.

1.S. Upon information and belief, Defendant Caraco is a Michigan corporation having a place of business at 1150 Elijah McCoy Drive, Detroit, Michigan 48202. Upon information and belief, Caraco manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

1.T. Upon information and belief, Defendant Sun Ltd. is an Indian corporation having a place of business at Acme Plaza, Andheri - Kurla Rd, Andheri (E), Mumbai - 400 059 and a manufacturing facility in Cranbury, New Jersey. Upon information and belief, Defendant Sun Ltd. itself and through its agent Defendant Caraco manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

1.U. Upon information and belief, Defendant Watson Pharmaceuticals is a Nevada corporation and parent, agent and alter-ego of Defendant Watson Laboratories having a place of business at 360 Mt. Kemble Avenue, Morristown, New Jersey 07962. Upon information and belief, Defendant Watson Pharmaceuticals markets numerous drugs throughout the United States, including in this judicial district.

1.V. Upon information and belief, Defendant Watson Laboratories is a Nevada corporation having a place of business at 311 Bonnie Circle, Corona, California 92880. Upon information and belief, Defendant Watson Laboratories manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

Nature of the Action

2. This is a civil action for the infringement of United States Patent No. 6,100,274 ("the '274 patent") and United States Patent No. 6,979,463 ("the '463 patent"). This action is based upon the Patent Laws of the United States, 35 U.S.C. §1 *et seq.*

Jurisdiction and Venue

3. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

4. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, a tortious act of patent infringement that has led to foreseeable harm and injury to a New Jersey corporation, Plaintiff Schering, in New Jersey. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

5. This Court has personal jurisdiction over Defendant Zydus by virtue of the fact that, *inter alia*, Zydus is a New Jersey corporation.

6. This Court has personal jurisdiction over Defendant Sandoz by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

7. This Court has personal jurisdiction over Defendant Mylan by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

8. This Court has personal jurisdiction over Defendant Orgenus by virtue of the fact that, *inter alia*, Orgenus is a New Jersey corporation.

9. This Court has personal jurisdiction over Defendant Orchid Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

10. This Court has personal jurisdiction over Defendant L. Perrigo by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

11. This Court has personal jurisdiction over Defendant Perrigo Co. by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

12. This Court has personal jurisdiction over Defendant Glenmark USA by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

13. This Court has personal jurisdiction over Defendant Glenmark Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey through its appointed agent and its subsidiary, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

14. This Court has personal jurisdiction over Defendant GeoPharma by virtue of, *inter alia*: (1) its specific contacts with New Jersey in connection with this case; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiaries, agents and alter-egos.

15. This Court has personal jurisdiction over Defendant Belcher by virtue of, *inter alia*: (1) its specific contacts with New Jersey in connection with this case; and (2) its systematic and continuous contacts with New Jersey through its parent, agent and alter-ego.

16. This Court has personal jurisdiction over Defendant Lupin Pharmaceuticals by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

17. This Court has personal jurisdiction over Defendant Lupin Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

18. This Court has personal jurisdiction over Defendant Ranbaxy Inc. by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

19. This Court has personal jurisdiction over Defendant Ranbaxy Laboratories by virtue of, *inter alia*: (1) its presence in New Jersey through its subsidiary, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

20. This Court has personal jurisdiction over Defendant DRLI by virtue of the fact that, *inter alia*, DRLI is a New Jersey corporation.

21. This Court has personal jurisdiction over Defendant DRLL by virtue of, *inter alia*: (1) its presence in New Jersey, including through its subsidiary, agent and alter ego; and (2) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego.

22. This Court has personal jurisdiction over Defendant Caraco by virtue of, *inter alia*, its systematic and continuous contacts with New Jersey.

23. This Court has personal jurisdiction over Defendant Sun Ltd. by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey, including through its agents and operating entities.

24. This Court has personal jurisdiction over Defendant Watson Pharmaceuticals, Inc. by virtue of, *inter alia*: (1) its presence in New Jersey; and (2) its systematic and continuous contacts with New Jersey.

25. This Court has personal jurisdiction over Defendant Watson Laboratories by virtue of, *inter alia*: (1) its presence in New Jersey through its parent, agent and alter-ego; (2) its systematic and continuous contacts with New Jersey, including through its parent, agent and alter-ego.

26. Venue is proper in this judicial district as to each defendant pursuant to 28 U.S.C. §§ 1391(b), (c) and/or (d) and 1400(b).

The Patents

27. On August 8, 2000, the '274 patent, titled "8-Chloro-6,11-Dihydro-11-(4-Piperidylidine)-5H-Benzo[5,6]Cyclohepta[1,2-b]Pyridine Oral Compositions," was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '274 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '274 patent is attached hereto as Exhibit A.

28. On December 27, 2005, the '463 patent, titled "Stable Extended Release Oral Dosage Composition," was duly and legally issued to Schering as assignee. Since that time, Schering has been, and continues to be, the sole owner of the '463 patent and the sole owner of the right to sue and to recover for any infringement of that patent. A copy of the '463 patent is attached hereto as Exhibit B.

Acts Giving Rise to this Action

Count I – Infringement of the '274 Patent by all Defendants

29. Upon information and belief, on or after June 21, 2006, Defendants submitted Abbreviated New Drug Applications ("ANDAs") 78-351 through 78-362, 78-364, 78-366 and 78-367 to the U.S. Food and Drug Administration ("FDA") under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). These ANDAs seek the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic versions of certain Schering Clarinex® brand desloratadine products. ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 specifically seek FDA approval to market the proposed generic versions of Schering's Clarinex® brand products prior to the expiration of the '274 patent.

30. ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations between August 17, 2006 and August 31, 2006.

31. Defendants' submission of ANDAs 78-351 through 78-362, 78-364, 78-366 and 78-367 to the FDA, including their § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if any of the Defendants commercially uses, offers for sale or sells a proposed generic version of a Schering Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

32. Schering will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count II – Infringement of the '274 Patent by Defendant Zydus

33. Upon information and belief, on or after June 21, 2006, Zydus submitted ANDAs 78-353 and 78-354 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-353 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-353 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent. ANDA 78-354 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of desloratadine per tablet. ANDA 78-354 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 2.5 and 5 milligram orally disintegrating tablet products prior to the expiration of the '274 patent.

34. ANDAs 78-353 and 78-354 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDA 78-353 and its § 505(j)(2)(A)(vii)(IV) allegation on August 18, 2006 and of ANDA 78-354 and its § 505(j)(2)(A)(vii)(IV) allegation on August 17, 2006.

35. Zydus's submission of ANDAs 78-353 and 78-354 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274 patent under 35

U.S.C. § 271(e)(2)(A). Moreover, if Zydus commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

36. Schering will be irreparably harmed by Defendant Zydus's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count III – Infringement of the '274 Patent by Defendant Sandoz

37. Upon information and belief, on or after June 21, 2006, Defendant Sandoz submitted ANDA 78-364 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-364 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-364 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

38. ANDA 78-364 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-364 and its § 505(j)(2)(A)(vii)(IV) allegation on August 30, 2006.

39. Sandoz's submission of ANDA 78-364 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Sandoz commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

40. Schering will be irreparably harmed by Defendant Sandoz's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count IV– Infringement of the '274 Patent by Defendant Mylan

41. Upon information and belief, on or after June 21, 2006, Defendant Mylan submitted ANDA 78-351 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-351 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-351 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

42. ANDA 78-351 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-351 and its § 505(j)(2)(A)(vii)(IV) allegation on August 23, 2006.

43. Mylan's submission of ANDA 78-351 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Mylan commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

44. Schering will be irreparably harmed by Defendant Mylan's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count V – Infringement of the '274 Patent by Defendants Orgenus and Orchid Ltd.

45. Upon information and belief, on or after June 21, 2006, Defendant Orchid Ltd., through its subsidiary, agent and alter-ego Defendant Orgenus, submitted ANDAs 78-356 and 78-357 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-357 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-357 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent. ANDA 78-356 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of desloratadine per tablet. ANDA 78-356 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 2.5 and 5 milligram orally disintegrating tablet products prior to the expiration of the '274 patent.

46. ANDAs 78-356 and 78-357 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations on August 30, 2006.

47. Orchid Ltd.'s submission of ANDAs 78-356 and 78-357 to the FDA through its subsidiary, agent and alter-ego Orgenus, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orchid Ltd. and/or Orgenus commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

48. Orgenus is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Orgenus participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

49. Orgenus's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orgenus commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

50. Schering will be irreparably harmed by Defendant Orchid Ltd.'s and Defendant Orgenus's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count VI – Infringement of the '274 Patent by Defendants L. Perrigo and Perrigo Co.

51. Upon information and belief, on or after June 21, 2006, Defendant Perrigo Co. submitted ANDA 78-361 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-361 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-361 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

52. ANDA 78-361 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by

the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-361 and its § 505(j)(2)(A)(vii)(IV) allegation on August 29, 2006.

53. Perrigo Co.'s submission of ANDA 78-361 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Perrigo Co. commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

54. Perrigo Co.'s subsidiary, agent and alter-ego Defendant L. Perrigo is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, L. Perrigo participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-361 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, L. Perrigo will, without authority, manufacture its proposed generic version of Schering's Clarinex® brand product in the United States and/or sell it to Perrigo Co. within the United States for subsequent commercial sale by Perrigo Co. If ANDA 78-361 is approved by the FDA.

55. L. Perrigo's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-361 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if L. Perrigo commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

56. Schering will be irreparably harmed by Defendant Perrigo Co.'s and Defendant L. Perrigo's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count VII – Infringement of the '274 Patent by Defendants Glenmark USA and Glenmark Ltd.

57. Upon information and belief, on or after June 21, 2006, Defendant Glenmark Ltd. submitted ANDA 78-362 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-362 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-362 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

58. ANDA 78-362 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-362 and its § 505(j)(2)(A)(vii)(IV) allegation on August 30, 2006.

59. Glenmark Ltd.'s submission of ANDA 78-362 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Glenmark Ltd. commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

60. Glenmark Ltd.'s subsidiary, agent and alter-ego Defendant Glenmark USA is jointly and severally liable for any infringement of the '274 patent. This is so because, upon

information and belief, Glenmark USA participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-362 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, Glenmark USA will, without authority, market and/or distribute its proposed generic version of Schering's Clarinex® brand product in the United States if ANDA 78-362 is approved by the FDA.

61. Glenmark USA's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-362 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Glenmark USA commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

62. Schering will be irreparably harmed by Defendant Glenmark Ltd.'s and Defendant Glenmark USA's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count VIII – Infringement of the '274 Patent by Defendants GeoPharma and Belcher

63. Upon information and belief, on or after June 21, 2006, Defendant GeoPharma, through its subsidiary, agent and alter-ego Defendant Belcher, submitted ANDA 78-355 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-355 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-355 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

64. ANDA 78-355 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-355 and its § 505(j)(2)(A)(vii)(IV) allegation on August 22, 2006.

65. GeoPharma's submission of ANDA 78-355 to the FDA, through Belcher, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if GeoPharma commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

66. Belcher is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Belcher participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-355 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

67. Belcher's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-355 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Belcher commercially manufactures, uses, offers for sale or sells the proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

68. Schering will be irreparably harmed by Defendant GeoPharma's and Defendant Belcher's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count IX – Infringement of the '274 Patent by Defendants Lupin Pharmaceuticals and Lupin Ltd.

69. Upon information and belief, on or after June 21, 2006, Defendant Lupin Ltd., through its subsidiary, agent and alter-ego Lupin Pharmaceuticals, submitted ANDA 78-352 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-352 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-352 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

70. ANDA 78-352 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-352 and its § 505(j)(2)(A)(vii)(IV) allegations on August 31, 2006.

71. Lupin Ltd.'s submission of ANDA 78-352 to the FDA, through Lupin Pharmaceuticals, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Ltd. commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

72. Lupin Pharmaceuticals is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Lupin Pharmaceuticals participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-352

and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, Lupin Pharmaceuticals will, without authority, market and/or distribute its proposed generic version of Schering's Clarinex® brand product in the United States if ANDA 78-352 is approved by the FDA.

73. Lupin Pharmaceuticals' participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-352 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Pharmaceuticals commercially manufactures, uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

74. Schering will be irreparably harmed by Defendant Lupin Ltd.'s and Defendant Lupin Pharmaceuticals' infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count X – Infringement of the '274 Patent
By Defendants Ranbaxy Inc. and Ranbaxy Ltd.

75. Upon information and belief, on or after June 21, 2006, Defendant Ranbaxy Ltd., through its subsidiary, agent and alter-ego Ranbaxy Inc., submitted ANDA 78-360 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-360 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-360 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

76. ANDA 78-360 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-360 and its § 505(j)(2)(A)(vii)(IV) allegation on August 18, 2006.

77. Ranbaxy Ltd.'s submission of ANDA 78-360 to the FDA, through Ranbaxy Inc., including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Ranbaxy Ltd. commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

78. Ranbaxy Inc. is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Ranbaxy Inc. participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-360 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

79. Ranbaxy Inc.'s participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-360 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Ranbaxy Inc. commercially manufactures, uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

80. Schering will be irreparably harmed by Defendant Ranbaxy Ltd.'s and Defendant Ranbaxy Inc.'s infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XI – Infringement of the '274 Patent by Defendants DRLI and DRLL

81. Upon information and belief, on or after June 21, 2006, Defendant DRLL, through its subsidiary, agent and alter-ego Defendant DRLI, submitted ANDAs 78-366 and 78-367 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-366 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine / 240 milligrams of pseudoephedrine per tablet. ANDA 78-366 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product prior to the expiration of the '274 patent. ANDA 78-367 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of desloratadine per tablet. ANDA 78-367 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 2.5 and 5 milligram orally disintegrating tablet products prior to the expiration of the '274 patent.

82. ANDAs 78-366 and 78-367 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic versions of Schering's Clarinex® brand products. Schering received written notification of ANDAs 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations on August 28, 2006.

83. DRLL's submission of ANDAs 78-366 and 78-367 to the FDA, through DRLI, including the § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '274

patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLL commercially uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

84. DRLI is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, DRLI participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

85. DRLI's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDAs 78-366 and 78-367 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLI commercially manufactures, uses, offers for sale or sells its proposed generic versions of Schering's Clarinex® brand products within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

86. Schering will be irreparably harmed by Defendant DRLL's and Defendant DRLI's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XII – Infringement of the '463 Patent by Defendants DRLI and DRLL

87. Upon information and belief, on or after June 21, 2006, Defendant DRLL, through its subsidiary, agent and alter-ego Defendant DRLI, submitted ANDA 78-366 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-366 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine / 240 milligrams of

pseudoephedrine per tablet. ANDA 78-366 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product prior to the expiration of the '463 patent.

88. ANDA 78-366 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '463 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product. Schering received written notification of ANDA 78-366 and its § 505(j)(2)(A)(vii)(IV) allegations on August 28, 2006.

89. DRLL's submission of ANDA 78-366, through Defendant DRLI, to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '463 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLL commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product, or induces or contributes to such conduct, it would further infringe the '463 patent under 35 U.S.C. § 271(a), (b) and/or (c).

90. DRLI is jointly and severally liable for any infringement of the '463 patent. This is so because, upon information and belief, DRLI participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-366 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA.

91. DRLI's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA 78-366 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA constitutes infringement of the '463 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if DRLI commercially manufactures, uses, offers for sale or sells its proposed generic version of

Schering's Clarinex® brand 5 milligram desloratadine / 240 milligram pseudoephedrine tablet product within the United States, or induces or contributes to any such conduct, it would further infringe the '463 patent under 35 U.S.C. § 271(a), (b) and/or (c).

92. Schering will be irreparably harmed by Defendant DRLL's and Defendant DRLI's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XIII – Infringement of the '274 Patent by Defendants Caraco and Sun Ltd.

93. Upon information and belief, on or after June 21, 2006, Defendant Sun Ltd. submitted ANDA 78-359 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-359 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-359 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

94. ANDA 78-359 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-359 and its § 505(j)(2)(A)(vii)(IV) allegation on August 28, 2006.

95. Sun Ltd.'s submission of ANDA 78-359 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Sun Ltd. commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand products, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

96. Defendant Caraco is jointly and severally liable for any infringement of the '274 patent. This is so because, upon information and belief, Caraco participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-359 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Additionally, upon information and belief, Caraco will, without authority, market and/or distribute its proposed generic version of Schering's Clarinex® brand product in the United States if ANDA 78-359 is approved by the FDA.

97. Schering will be irreparably harmed by Defendant Sun Ltd.'s and Defendant Caraco's infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Count XIV – Infringement of the '274 Patent by Defendants Watson Pharmaceuticals and Watson Laboratories

98. Upon information and belief, on or after June 21, 2006, Defendant Watson Laboratories submitted ANDA 78-358 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). ANDA 78-358 seeks the FDA approval necessary to engage in the commercial manufacture, use, offer for sale and sale of generic tablets containing 5 milligrams of desloratadine per tablet. ANDA 78-358 specifically seeks FDA approval to market a proposed generic version of Schering's Clarinex® brand desloratadine 5 milligram tablet product prior to the expiration of the '274 patent.

99. ANDA 78-358 alleges under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use or sale of the proposed generic version of Schering's Clarinex® brand product. Schering received written notification of ANDA 78-358 and its § 505(j)(2)(A)(vii)(IV) allegation on August 25, 2006.

100. Watson Laboratories' submission of ANDA 78-358 to the FDA, including the § 505(j)(2)(A)(vii)(IV) allegation, constitutes infringement of the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Watson Laboratories commercially uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product, or induces or contributes to such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

101. Upon information and belief, Watson Laboratories' parent, agent and alter-ego Defendant Watson Pharmaceuticals participated in, contributed to, aided, abetted and/or induced the submission of ANDA 78-358 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA. Watson Pharmaceuticals' submission of ANDA 78-358 and its § 505(j)(2)(A)(vii)(IV) allegation to the FDA infringed the '274 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Watson Pharmaceuticals commercially manufactures, uses, offers for sale or sells its proposed generic version of Schering's Clarinex® brand product within the United States, or induces or contributes to any such conduct, it would further infringe the '274 patent under 35 U.S.C. § 271(a), (b) and/or (c).

102. Schering will be irreparably harmed by Defendant Watson Laboratories' and Defendant Watson Pharmaceuticals' infringing activities unless those activities are enjoined by this Court. Schering does not have an adequate remedy at law.

Prayer for Relief

WHEREFORE, Schering prays for judgment as follows:

A. That all Defendants have infringed the '274 patent and Defendants DRLI and DRLL have infringed the '463 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of any of Defendants' ANDAs identified in this Complaint shall not be earlier than the expiration date of the respective '274 patent or '463 patent, including any extensions;

C. That Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale or selling the proposed generic versions of Schering's Clarinex® brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '274 patent, prior to the expiration of the '274 patent, including any extensions;

D. That Defendants DRLI and DRLL, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale or selling the proposed generic versions of Schering's Clarinex® brand products identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '463 patent, prior to the expiration of the '463 patent, including any extensions;

E. That Schering be awarded monetary relief if any Defendant commercially uses, offers for sale or sells its proposed generic version of a Schering Clarinex®

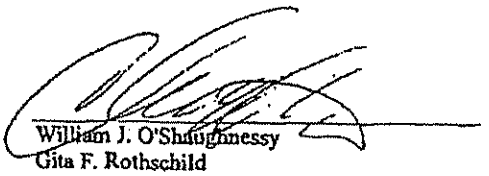
brand product, or any other product that infringes or induces or contributes to the infringement of the '274 or '463 patents, within the United States prior to the expiration of that patent, including any extensions, and that any such monetary relief be awarded to Schering with prejudgment interest;

F. That Schering be awarded the attorney fees, costs and expenses that it incurs prosecuting this action; and

G. That Schering be awarded such other and further relief as this Court deems just and proper.

Dated: September 29, 2006

Respectfully submitted,



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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: DESLORATADINE PATENT LITIGATION	MDL No.: 1851 Case No. 3:07-CV-3930 (MLC)(TJB) CIVIL ACTION ELECTRONICALLY FILED
SCHERING CORPORATION, Plaintiff, v. ZYDUS PHARMACEUTICALS, USA, INC., et al., Defendants.	Case No. 3:06-CV-4715 (MLC)(TJB) CIVIL ACTION **ORCHID CHEMICALS & PHARMACEUTICALS LTD.'S AMENDED ANSWER AND COUNTERCLAIMS**

STATEMENT PURSUANT TO L. CIV. R. 10.1

Defendant Corporation Orchid Chemicals & Pharmaceuticals, Ltd. is an Indian corporation, with its principal place of business located at Orchid Towers, #313, Valluvar Kottam High Road, Nungambakkam, Chennai - 600 034, Tamil Nadu, India.

AMENDED ANSWER

Defendants Orchid Chemicals & Pharmaceuticals, Ltd. and Orgenus Pharma, Inc. (collectively "Orchid") hereby answer the Amended Complaint of plaintiff Schering Corporation ("Schering") and counterclaim as follows:

THE PARTIES

1.A. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 1.A.

1.B. – 1.D. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 1.B. – 1.D., which pertain solely to other Defendants.

1.E. Orchid admits that Defendant Orgenus is a New Jersey corporation and wholly-owned subsidiary of Defendant Orchid Ltd. having a place of business at 700 Alexander Park, Suite 104, Princeton, New Jersey 08540. Orchid denies the remaining allegations of paragraph 1E.

1.F. Orchid admits the allegations of paragraph 1.F.

1.G. – 1.V. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 1.G. – 1.V., which pertain solely to other Defendants.

NATURE OF ACTION

2. In responding to paragraph 2, Orchid admits that Schering purports to bring this action under Title 35, United States Code § 1 *et. seq.*, but Orchid expressly denies liability thereunder.

JURISDICTION AND VENUE

3. In responding to paragraph 3, Orchid admits that, with respect to the claims against it, this Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), but Orchid expressly denies liability thereunder.

4. – 26. Orchid states that the allegations in paragraphs 4 – 26 are conclusions of law as to which no response is required.

THE PATENTS

27. Orchid admits that United States Patent No. 6,100,274 ("the '274 patent") states on its face that it was issued to Schering by the United States Patent and Trademark Office. Orchid denies that the '274 patent was "duly and legally issued" by the United States Patent and Trademark Office. Orchid lacks sufficient information as to the remaining allegations in paragraph 27, and, on that basis, denies each and every remaining allegation.

28. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraph 28, which pertain solely to other Defendants. U.S. Pat. No. 6,979,463 has not been asserted against Orchid.

Count I – Alleged Infringement of the '274 Patent by All Defendants

29. Orchid admits that it submitted Abbreviated New Drug Applications ("ANDAs") 78-356 and 78-357 for approval to engage in the commercial manufacture, use, and sale of generic versions of certain Schering Clarinex® brand desloratadine products before the expiration of the '274 patent. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 29, which pertain solely to other Defendants.

30. Orchid admits that in a letter dated August 25, 2006, it notified plaintiff that Orchid had filed ANDAs No. 78-356 and 78-357 pursuant to section 505(j), Title 21 of the Federal Food, Drug & Cosmetic Act ("the Act") in order to obtain approval to engage in the commercial manufacture, use, or sale of generic versions of Schering's Clarinex® brand products. Orchid refers to the letter for its contents. Orchid admits that its ANDAs 78-356 and 78-357 assert that the claims of the '274 patent are either invalid or not infringed by the generic drug products set forth in those ANDAs. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 30, which pertain solely to other Defendants.

31. Orchid denies the allegations of paragraph 31 as to ANDAs 78-356 and 78-357. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 31, which pertain solely to other Defendants.

32. Orchid denies the allegations of paragraph 32 as to Orchid. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the remaining allegations contained in paragraph 32, which pertain solely to other Defendants.

Count II – Alleged Infringement of the '274 Patent by Defendant Zydus

33. – 36. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 33 - 36, which pertain solely to another Defendant.

Count III – Alleged Infringement of the '274 Patent by Defendant Sandoz

37. – 40. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 37 - 40, which pertain solely to another Defendant.

Count IV – Alleged Infringement of the '274 Patent by Defendant Mylan

41. – 44. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 41 - 44, which pertain solely to another Defendant.

Count V – Alleged Infringement of the '274 Patent by Defendants Orgenus and Orchid Ltd.

45. Orchid denies the allegations of paragraph 45.

46. Orchid admits that ANDAs 78-356 and 78-357 allege under § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act that the claims of the '274 patent are either invalid or not infringed by the manufacture, use, or sale of the proposed generic versions of Schering's Clarinex® brand products. Orchid admits that it provided written notification to Schering of ANDAs 78-356 and 78-357 and its 505(j)(2)(A)(vii)(IV) allegations in letters dated August 25, 2006.

47. Orchid denies the allegations of paragraph 47.

48. Orchid denies the allegations of paragraph 48.

49. Orchid denies the allegations of paragraph 49.

50. Orchid denies the allegations of paragraph 50.

Count VI – Alleged Infringement of the '274 Patent by Defendants L. Perrigo and Perrigo Co.

51. – 56. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 51 - 56, which pertain solely to other Defendants.

Count VII – Alleged Infringement of the '274 Patent by Defendants Glenmark USA and Glenmark Ltd.

57. – 62. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 57 - 62, which pertain solely to other Defendants.

Count VIII – Alleged Infringement of the '274 Patent by Defendants GeoPharma and Belcher

63. – 68. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 63 - 68, which pertain solely to other Defendants.

Count IX – Alleged Infringement of the '274 Patent by Defendants Lupin Pharmaceuticals and Lupin Ltd.

69. – 74. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 69 - 74, which pertain solely to other Defendants.

Count X – Alleged Infringement of the '274 Patent by Defendants Ranbaxy Inc. and Ranbaxy Ltd.

75. – 80. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 75 – 80, which pertain solely to other Defendants.

Count XI – Alleged Infringement of the '274 Patent by Defendants DRLI and DRLL

81. – 86. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 81 - 86, which pertain solely to other Defendants.

Count XII – Alleged Infringement of the '463 Patent by Defendants DRLI and DRLL

87. – 92. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 87 - 92, which pertain solely to other Defendants.

Count XIII – Alleged Infringement of the '274 Patent by Defendants Caraco and Sun Ltd.

93. – 98. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 93 - 98, which pertain solely to other Defendants.

Count XIV – Alleged Infringement of the '274 Patent by Defendants Watson Pharmaceuticals and Watson Laboratories

99. – 104. Orchid is without knowledge or information sufficient to form a belief as to the truth or falsity of the allegations contained in paragraphs 99 - 104, which pertain solely to other Defendants.

Response to Prayer for Relief

Orchid denies that Schering is entitled to any of the relief that it seeks in the prayer. Further answering Schering's Amended Complaint, Orchid alleges as follows:

AFFIRMATIVE DEFENSES

First Affirmative Defense

Orchid has not infringed, is not infringing, and will not infringe (directly, indirectly, contributorily or by inducement) any valid claim of the '274 patent.

Second Affirmative Defense

By reason of the prior art and/or statements and representations made to the United States Patent and Trademark Office during the prosecution of the application that led to the issuance of the '274 patent, the patent is so limited that no claim can be construed as covering any Orchid activity.

Third Affirmative Defense

Each and every asserted claim of the '274 patent placed in issue herein is invalid and void for failure to meet the requirements of Title 35, United States Code, including, *inter alia*, §§ 101, 102, 103, 112, and/or for double patenting.

Fourth Affirmative Defense

Plaintiff's case is not exceptional under 35 U.S.C. § 285.

Fifth Affirmative Defense

Each of Plaintiff's Counts alleging infringement of the '274 patent under § 271(a), (b), and/or (c) fail to state a claim upon which relief can be granted.

COUNTERCLAIMS

Defendants and Counterclaimants Orchid Chemicals & Pharmaceuticals, Ltd. and Orgenus Pharma, Inc. (collectively "Orchid") brings the following Counterclaims against Plaintiff and Counterdefendant Schering Corporation ("Schering").

Jurisdiction and Venue

1. This action arises under the Patent Laws of the United States, Title 35, United States Code, and the Food and Drug laws of the United States, Title 21, United States Code. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1338(a), 2201, and 2202.

2. Venue is proper under 28 U.S.C. §§ 1391 and 1400(b).

3. In its Amended Complaint filed on or about December 18, 2006 in this Court, plaintiff Schering has charged Orchid with infringement of the '274 patent. There is, therefore, a substantial, actual, and continuing controversy between Defendant and Counterclaimant Orchid and Plaintiff and Counterdefendant Schering with respect to the infringement and validity of the '274 patent.

Parties

4. Orchid Chemicals & Pharmaceuticals, Ltd. is an Indian corporation, having a principal place of business at Orchid Towers, #313, Valluvar Kottam High Road, Nungambakkam, Chennai - 600 034, Tamil Nadu, India.

5. Orgenus Pharma, Inc. is a New Jersey corporation and wholly-owned subsidiary of Defendant Orchid Ltd. having a place of business at 700 Alexander Park, Suite 104, Princeton, New Jersey 08540.

6. Defendant and Counterclaimant Orchid is informed and believes that Plaintiff and Counterdefendant Schering is a New Jersey corporation having places of business throughout New Jersey, including a place of business at 3070 Route 22 West, Branchburg, New Jersey 08876.

First Counterclaim – Declaration of Non-Infringement

7. Defendant and Counterclaimant Orchid repeats and realleges the allegations in Counterclaim paragraphs 1 through 6 hereof as though fully set forth herein.

8. Orchid does not infringe, has not infringed, and will not infringe (directly, indirectly, contributorily, or by inducement) any valid claim of United States Patent No. 6,100,274 ("the '274 patent").

Second Counterclaim – Declaration of Invalidity

9. Defendant and Counterclaimant Orchid repeats and realleges the allegations in Counterclaim paragraphs 1 through 8 hereof as though fully set forth herein.

10. Each and every claim of the '274 patent is invalid for failure to meet the requirements of Title 35, United States Code, including, *inter alia*, §§ 101, 102, 103 and 112.

Third Counterclaim – Delisting of the '274 Patent

11. Defendant and Counterclaimant Orchid repeats and realleges the allegations in Counterclaim paragraphs 1 through 10 hereof as though fully set forth herein.

12. This is a counterclaim under 21 U.S.C. § 355(j)(5)(C)(ii) for an order requiring Plaintiff and Counterdefendant Schering to delete the '274 patent from the Orange Book with respect to NDA 21-312 on the ground that the '274 patent does not claim either (i) the drug for which the application was approved, or (ii) an approved method of using the drug.

13. An applicants that submits a New Drug Application (NDA) is required to disclose to FDA "any patent which claims the drug for which the applicant submitted the application ... and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug." 21 U.S.C. § 355(B)(1). The statute directs FDA to list the disclosed patents, which FDA

does in a publication entitled "Approved Drug Products With Therapeutic Equivalence Evaluations," more commonly known as the "Orange Book."

14. An applicant that submits a Abbreviated New Drug Application (ANDA) for a generic drug referencing an NDA must make one of four certifications as to each patent listed in the Orange Book that purportedly claims the drug approved in the NDA. 21 U.S.C. § 355(j)(2)(A)(vii). When an ANDA applicant certifies that an Orange Book-listed patent is invalid or will not be infringed (a so-called "paragraph IV certification"), it must provide notice to the patentee and the holder of the approved NDA that it has submitted such a certification. *Id.* § 355(j)(2)(B)(i).

15. Once the patent holder receives notice that an ANDA applicant has filed a paragraph IV certification with respect to an approved drug, the patent holder has 45 days within which to file a patent infringement action. 21 U.S.C. § 355(j)(5)(B)(iii). If the patentee files an infringement action within the designated 45-day period, subject to certain exceptions, the FDA generally may not approve the ANDA until 30 months have passed. 21 U.S.C. § 355(j)(5)(B)(iii).

16. Plaintiff and Counterdefendant Schering has approved New Drug Applications (or "NDAs") for a variety of dosage forms of its CLARINEX® products. For example, NDA No. 021-165 relates to CLARINEX® 5 mg tablets, while NDA No. 021-312 relates to CLARINEX® 2.5 and 5 mg orally disintegrating tablets (marketed as "CLARINEX® RediTabs").

17. Schering caused the '274 patent to be listed on the Orange Book for both NDA No. 021-165 and NDA No. 021-312. Thus, any ANDA applicant seeking to market a generic version of desloratadine orally disintegrating tablets, for instance, has to submit a

certification relating to the '274 patent. Possible certifications include a statement that the ANDA applicant will not market its proposed generic product until the expiration of the '274 patent (which is slated to expire in 2020) or that the patent is invalid or will not be infringed.

18. Defendant Orchid filed an ANDA for desloratadine orally disintegrating tablets (No. 78-356), which referenced Plaintiff Schering's CLARINEX® RediTabs NDA, and included a paragraph IV certification for the '274 patent listed in the Orange Book. Orchid provided notice to Schering of the certification, Schering sued within the required 45-days, and now FDA presumptively is prevented from approving Orchid's ANDA for 30-months, or until about March 2009, absent prior action by this Court.

19. Schering improperly caused the FDA to list the '274 patent with regard to NDA No. 021-312 because the '274 patent does not cover CLARINEX® RediTabs. The '274 patent discloses and claims desloratadine compositions containing a basic salt. However, as the FDA-approved label for CLARINEX® RediTabs confirms, Schering's orally disintegrating formulation does not contain a basic salt. *June 26, 2002 Final Draft Labeling* at 1.

20. Orchid is in a position to enter the market for generic desloratadine orally disintegrating tablets but for the presumptive 30-month stay associated with Schering's filing of the instant lawsuit relating to Orchid ANDA No. 78-356. Thus, as Schering is aware, Orchid has fully and finally resolved a separate lawsuit with another pharmaceutical company involving another patent listed in the Orange Book for NDA No. 21-312 and another listed patent has expired. Orchid expects to obtain tentative approval to market its generic desloratadine orally disintegrating tablets in the near future. In short, the 30-month stay is the only remaining barrier to the availability of generic desloratadine orally disintegrating tablets to the public.

21. Concerned that pharmaceutical companies might improperly list patents in the Orange Book to thwart potential generic entry, Congress has specifically authorized courts to issue an order that the NDA holder "correct or delete the patent information submitted by the holder . . . on the ground that the patent does not claim either—(aa) the drug for which the application was approved; or (bb) the approved method of using the drug." 21 U.S.C. § 355(j)(5)(C)(ii).

22. Orchid is entitled to an order that Schering be ordered to delete the '274 patent from the Orange Book with respect to NDA No. 21-312 on the grounds that the '274 patent neither claims the drug for which NDA No. 21-312 was approved nor an approved method of using the drug.

Fourth Counterclaim – Declaration of Exceptional Case

23. Defendant and Counterclaimant Orchid repeats and realleges the allegations in Counterclaim paragraphs 1 through 23 hereof as though fully set forth herein.

24. This case is exceptional under 35 U.S.C. § 285.

Prayer for Judgment

WHEREFORE, Orchid prays for the following relief:

A. That all claims against Defendant/Counterclaimant Orchid be dismissed with prejudice and that all relief requested by Plaintiff/Counterdefendant Schering be denied;

B. That a judgment be entered declaring that Defendant/Counterclaimant Orchid does not infringe, has not infringed, and will not infringe any valid claim of United States Patent No. 6,100,274, and that Orchid has a lawful right to continue with ANDA Nos. 78-356 and 78-357 for desloratadine tablets, and further that Defendant/Counterclaimant Orchid has a lawful right to manufacture, market, and/or sell their desloratadine tablets once approved by the FDA;

C. That a judgment be entered declaring that the claims of United States Patent No. 6,100,274 is invalid;

D. That an order be entered requiring Schering to delete United States Patent No. 6,100,274 patent from the Orange Book with respect to NDA 21-312;

E. That an order be entered that ANDA No. 78-356 is not subject to a stay of approval pursuant to 35 U.S.C. § 355(j)(5)(B)(iii) based on U.S. Patent No. 6,100,274.

F. Finding this case to be exceptional pursuant to 35 U.S.C. § 285 and imposing sanctions for the entire costs, attorney fees and expenses that Orchid incurs in this action;

G. That a judgment be entered that this action is an exceptional case pursuant to 35 U.S.C. § 285 and that Defendant/Counterclaimant Orchid is therefore entitled to a recovery of its reasonable attorneys fees upon prevailing in this action;

H. That Defendant/Counterclaimant Orchid be awarded costs, attorneys fees and other relief, both legal and equitable, to which it may be justly entitled; and

I. That Defendant/Counterclaimant Orchid be awarded such other and further relief as this Court deems just and proper.

Dated: April 16, 2008

s/ R. Christopher Owens
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Attorneys for defendants Orchid Chemicals & Pharmaceuticals, Ltd. and Orgenus Pharma, Inc.

CERTIFICATION PURSUANT TO L. CIV. R. 11.2

I hereby certify that to the best of my knowledge the specific matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding. However, Defendants Orchid Chemicals & Pharmaceuticals, Ltd. and Orgenus, Inc. hereby provide notice of pendency in this District of an action related to this case. Specifically, the action entitled *Sepracor Inc. v. Orchid Chemicals & Pharmaceutical, Ltd.*, 07-CV-04623-MLC-TJB, currently pending before this Court, is related to this action under L.Civ. Rule 40.1(c). Both this case and *Sepracor Inc. v. Orchid Chemicals & Pharmaceuticals, Ltd.* relate to patent infringement claims arising out of the filing by Orchid Chemicals & Pharmaceuticals Ltd. of ANDA Nos. 78-356 and 78-357.

Dated: April 16, 2008

s/ R. Christopher Owens
R. Christopher Owens

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UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IN RE: DESLORATADINE PATENT LITIGATION	MDL No.: 1851 Case No. 3:07-CV-3930 (MLC)(TJB) CIVIL ACTION ELECTRONICALLY FILED
SCHERING CORPORATION, Plaintiff, v. ZYDUS PHARMACEUTICALS, USA, INC., et al., Defendants.	Case No. 3:06-CV-4715 (MLC)(TJB) CIVIL ACTION **CERTIFICATE OF SERVICE**

I, R. Christopher Owens, hereby certify under the penalty of perjury that:

1. I am an attorney-at-law of the state of New Jersey and am associated with the law firm of Latham & Watkins LLP, attorneys for Defendants Orchid Chemicals & Pharmaceuticals Ltd. and Orgenus Pharma, Inc. ("Orchid") in the above-captioned matter.

2. I am a member in good standing of the bar of this Court.

3. On this date, I filed **ORCHID CHEMICALS & PHARMACEUTICALS LTD.'S**

AMENDED ANSWER AND COUNTERCLAIMS via the CM/ECF system, thereby effectuating service upon all counsel of record.

4. I further certify that on this date, a true and correct copy of the aforementioned document was served by first class mail, postage prepaid, upon counsel for Plaintiff at the following addresses:

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Fax 973.297.3722

Attorneys for Plaintiff Schering Corporation

I hereby certify, under penalty of perjury, that the statements made herein are true and correct.

Dated: April 16, 2008

s/ R. Christopher Owens
R. Christopher Owens

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SEPRACOR INC. and UNIVERSITY OF MASSACHUSETTS, **Plaintiffs,** **v.** **ORCHID CHEMICALS & PHARMACEUTICALS LTD., ORCHID HEALTHCARE, and ORGENUS PHARMA, INC.** **Defendants.**	**Civil Action No.:** **COMPLAINT FOR PATENT INFRINGEMENT** **(Filed Electronically)**

Plaintiffs Sepracor Inc. ("Sepracor") and University of Massachusetts ("UMass"), by their attorneys, for their Complaint against Defendants Orchid Chemicals & Pharmaceuticals Ltd. ("Orchid Ltd."), Orchid Healthcare, and Orgenus Pharma, Inc. ("Orgenus") hereby allege as follows:

Nature of the Action

1. This is an action for patent infringement arising under the patent laws of the United States, 35 U.S.C. § 100 *et seq.*, arising from Defendants' filing of Abbreviated New

Drug Applications ("ANDA") with the United States Food and Drug Administration ("FDA") seeking approval to commercially market generic versions of the patented Clarinex® drug products prior to the expiration of United States Patent Nos. 7,211,582 ("the '582 patent"), 7,214,683 ("the '683 patent") and 7,214,684 ("the '684 patent"), which are owned by Sepracor and UMass.

The Parties

2. Plaintiff Sepracor is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 84 Waterford Drive, Marlborough, Massachusetts 01752.

3. Plaintiff UMass is a public institution of higher education of the Commonwealth of Massachusetts, having a place of business at 55 Lake Avenue North, Worcester, Massachusetts 01655.

4. Upon information and belief, Orchid Ltd. is a corporation organized and existing under the laws of India, having a place of business at Plot No. B3-B6 & B11-B14, Sipcot Industrial Park, Irungattukottai, Sriperumbudur (TK) – 602 105, Kancheepuram District, Tamil Nadu, India. Upon information and belief, Orchid Ltd. is registered to do business in New Jersey and maintains a registered agent in New Jersey for the receipt of service of process.

5. Upon information and belief, Orchid Healthcare is a division and an agent and alter-ego of Orchid Ltd., having a place of business at #313, Valluvar Kottam High Road, Nungambakkam, Chennai – 600 034, India and/or Plot No. B3-B6 & B11-B14, Sipcot Industrial Park, Irungattukottai, Sriperumbudur (TK) – 602 105, Kancheepuram District, Tamil Nadu, India.

6. Upon information and belief, Orgenus is a New Jersey corporation and a wholly owned subsidiary, agent and alter-ego of Orchid Ltd., having a place of business at 116 Village Boulevard, Suite 200, Princeton, New Jersey 08540.

7. Orchid Ltd. and Orchid Healthcare are referred to hereinafter, collectively, as "Orchid."

8. Upon information and belief, Orchid is in the business of manufacturing generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies.

9. Upon information and belief, Orchid, with the participation of Orgenus, prepared, assembled and caused to be filed with the FDA, pursuant to 21 U.S.C. § 355(j), ANDA No. 78-356 concerning generic versions of orally disintegrating tablets containing 2.5 and 5 milligrams of Clarinex® brand desloratadine per tablet and ANDA No. 78-357 concerning generic versions of tablets containing 5 milligrams of Clarinex® brand desloratadine per tablet (these generic tablets are collectively referred to herein as "Orchid's Proposed Products").

10. Upon information and belief, if either ANDA No. 78-356 or ANDA No. 78-357 or both are approved, it is the intention of Orchid to distribute Orchid's Proposed Products in the United States.

Jurisdiction and Venue

11. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

12. This court has personal jurisdiction over Orgenus because Orgenus is a New Jersey corporation.

13. This court has personal jurisdiction over Orchid by virtue of, *inter alia*: (1) its registration to do business in New Jersey; (2) its presence in New Jersey through its subsidiary, agent and alter-ego, Orgenus; and (3) its systematic and continuous contacts with New Jersey, including through its subsidiary, agent and alter-ego, Orgenus, and through Orchid Healthcare as agent and alter-ego. Further, upon information and belief, Orchid is in the business of manufacturing, marketing, importing into the United States and selling pharmaceutical drug products, including generic drug products. Upon information and belief, Orchid directly, or through its divisions, subsidiaries, agents and/or alter-egos, manufactures, markets and sells generic drugs throughout the United States and in this judicial district. Upon information and belief, Orchid purposefully has conducted and continues to conduct business, directly, and/or through its divisions, subsidiaries, agents and/or alter-egos in this judicial district, and this judicial district is a likely destination of Orchid's Proposed Products.

14. This Court also has personal jurisdiction over Orchid because Orchid has previously submitted to the jurisdiction of this Court. For example, in *Schering Corporation v. Zydus Pharmaceuticals, USA, Inc. et al.*, D.N.J., Civil Action No. 3:06-4715 (MLC) (TJB), Orchid consented to jurisdiction in New Jersey and filed certain counterclaims, thus availing itself of this Court's jurisdiction in connection with causes of action involving the same ANDAs at issue here, *i.e.*, Nos. 78-356 and 78-357.

15. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

The Patents In Suit and the Clarinex® Drug Products

16. On May 1, 2007, the '582 patent, entitled "Methods for Treating Urticaria Using Descarboethoxyloratadine," was duly and legally issued. Sepracor and UMass are

assignees of the entire right, title and interest in the '582 patent. A copy of the '582 patent is attached hereto as Exhibit A.

17. On May 8, 2007, the '683 patent, entitled "Compositions of Descarboethoxyloratadine," was duly and legally issued. Sepracor and UMass are assignees of the entire right, title and interest in the '683 patent. A copy of the '683 patent is attached hereto as Exhibit B.

18. On May 8, 2007, the '684 patent, entitled "Methods for the Treatment of Allergic Rhinitis," was duly and legally issued. Sepracor and UMass are assignees of the entire right, title and interest in the '684 patent. A copy of the '684 patent is attached hereto as Exhibit C.

19. The '582, '683 and '684 patents are identified in the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" in association with 5 milligram desloratadine tablets, which are sold as a commercial product under the trade name Clarinex®, and 2.5 and 5 milligram desloratadine orally disintegrating tablets, which are sold as a commercial product under the trade name Clarinex® RediTabs®. These patents cover approved uses of commercial Clarinex® and approved Clarinex® products.

Acts Giving Rise to this Action

20. Plaintiffs Sepracor and UMass received a letter from Orchid, dated August 13, 2007, notifying them that Orchid had filed with the FDA an ANDA (No. 78-356) under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) to obtain FDA approval to engage in the commercial manufacture, importation, use, offer for sale or sale of generic orally disintegrating tablets containing 2.5 and 5 milligrams of Clarinex® brand desloratadine per tablet.

21. Plaintiffs Sepracor and UMass received a second letter from Orchid, dated August 13, 2007 (collectively, these letters are referred to as "the Notification Letters"), notifying them that Orchid had filed with the FDA an ANDA (No. 78-357) under § 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 355(j)) to obtain FDA approval to engage in the commercial manufacture, importation, use, offer for sale or sale of generic tablets containing 5 milligrams of Clarinex® brand desloratadine per tablet.

22. Upon information and belief, Orchid intends to engage and will engage in the commercial manufacture, importation, use, offer for sale or sale of Orchid's Proposed Products promptly upon receiving FDA approval to do so.

23. The Notification Letters state that ANDA Nos. 78-356 and 78-357 contain a "Paragraph IV Certification" that, in Orchid's opinion, the '582, '683 and '684 patents are invalid and/or not infringed.

24. The Notification Letters do not provide a detailed basis for why the '582, '683 and '684 patents will not be infringed by the manufacture, importation into the United States, use, offer for sale, or sale of Orchid's Proposed Products.

25. Upon information and belief, ANDA Nos. 78-356 and 78-357 contain information showing that Orchid's Proposed Products: (a) are the bioequivalent to a patented Clarinex® 5 milligram tablet product; (b) are the bioequivalent to a patented Clarinex® RediTabs® orally disintegrating 2.5 or 5 milligram tablet; (c) have the same active ingredient as a patented Clarinex® product; (d) have the same route of administration and strength as a patented Clarinex® product; and (e) have the same, or substantially the same, proposed labeling, and the same indication and usage as a patented Clarinex® product.

26. This action is being brought pursuant to 21 U.S.C. § 355(j)(5)(B)(iii) before the expiration of forty-five days from the date of receipt of the Notification Letters.

Count I – Infringement of the '582 Patent by Defendant

27. Plaintiffs repeat and reallege the allegations of paragraphs 1-26 as though fully set forth herein.

28. Orchid's submission of ANDAs 78-356 and 78-357 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification to obtain approval to engage in the commercial manufacture, importation, use, offer for sale or sale of Orchid's Proposed Products, prior to the expiration of the '582 patent, constitutes infringement of one or more of the claims of the '582 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orchid and/or Orgenus commercially uses, offers for sale or sells any of Orchid's Proposed Products, or induces or contributes to such conduct, it would further infringe one or more claims of the '582 patent under 35 U.S.C § 271(a), (b) and/or (c).

29. Orgenus is jointly and severally liable for any infringement of one or more claims of the '582 patent. This is so because, upon information and belief, Orgenus participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

30. Unless enjoined by this Court, Orchid and Orgenus, upon FDA approval of ANDA No. 78-356 and/or ANDA No. 78-357, will infringe the '582 patent under 35 U.S.C. § 271 by making, using, importing, offering to sell, or selling Orchid's Proposed Products in the United States.

31. Orchid and Orgenus had notice of the '582 patent prior to undertaking their acts of infringement. Orchid and Orgenus' infringement of the '582 patent has been, and continues to be, willful and deliberate.

32. Plaintiffs will be substantially harmed if Orchid's and Orgenus' infringement of the '582 patent is not enjoined, and Plaintiffs are entitled to equitable relief.

Count II – Infringement of the '683 Patent by Defendant

33. Plaintiffs repeat and reallege the allegations of paragraphs 1-32 as though fully set forth herein.

34. Orchid's submission of ANDAs 78-356 and 78-357 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification to obtain approval to engage in the commercial manufacture, importation, use, offer for sale or sale of Orchid's Proposed Products, prior to the expiration of the '683 patent, constitutes infringement of one or more of the claims of the '683 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orchid and/or Orgenus commercially uses, offers for sale or sells any of Orchid's Proposed Products, or induces or contributes to such conduct, it would further infringe one or more claims of the '683 patent under 35 U.S.C § 271(a), (b) and/or (c).

35. Orgenus is jointly and severally liable for any infringement of one or more claims of the '683 patent. This is so because, upon information and belief, Orgenus participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

36. Unless enjoined by this Court, Orchid and Orgenus, upon FDA approval of ANDA No. 78-356 and/or ANDA No. 78-357, will infringe the '683 patent under 35 U.S.C. §

271 by making, using, importing, offering to sell, or selling Orchid's Proposed Products in the United States.

37. Orchid and Orgenus had notice of the '683 patent prior to undertaking their acts of infringement. Orchid's and Orgenus' infringement of the '683 patent has been, and continues to be, willful and deliberate.

38. Plaintiffs will be substantially harmed if Orchid and Orgenus' infringement of the '683 patent is not enjoined, and Plaintiffs are entitled to equitable relief.

Count III – Infringement of the '684 Patent by Defendant

39. Plaintiffs repeat and reallege the allegations of paragraphs 1-38 as though fully set forth herein.

40. Orchid's submission of ANDAs 78-356 and 78-357 to the FDA, including its § 505(j)(2)(A)(vii)(IV) certification to obtain approval to engage in the commercial manufacture, importation, use, offer for sale or sale of Orchid's Proposed Products, prior to the expiration of the '684 patent, constitutes infringement of one or more of the claims of the '684 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Orchid and/or Orgenus commercially uses, offers for sale or sells any of Orchid's Proposed Products, or induces or contributes to such conduct, it would further infringe one or more claims of the '684 patent under 35 U.S.C § 271(a), (b) and/or (c).

41. Orgenus is jointly and severally liable for any infringement of one or more claims of the '684 patent. This is so because, upon information and belief, Orgenus participated in, contributed to, aided, abetted and/or induced the submission of ANDAs 78-356 and 78-357 and their § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

42. Unless enjoined by this Court, Orchid and Orgenus, upon FDA approval of ANDA No. 78-356 and/or ANDA No. 78-357, will infringe the '684 patent under 35 U.S.C. § 271 by making, using, importing, offering to sell, or selling Orchid's Proposed Products in the United States.

43. Orchid and Orgenus had notice of the '684 patent prior to undertaking their acts of infringement. Orchid's and Orgenus' infringement of the '684 patent has been, and continues to be, willful and deliberate.

44. Plaintiffs will be substantially harmed if Orchid's and Orgenus' infringement of the '684 patent is not enjoined, and Plaintiffs are entitled to equitable relief.

Prayer for Relief

WHEREFORE, Plaintiffs respectfully request the following relief:

A. A Judgment declaring that Defendants have infringed one or more claims of the '582 patent;

B. A Judgment declaring that Defendants have infringed one or more claims of the '683 patent;

C. A Judgment declaring that Defendants have infringed one or more claims of the '684 patent;

D. An Order that the effective date of any FDA approval of ANDA No. 78-356 and/or ANDA No. 78-357 be no earlier than the date on which the '582 patent expires, including any regulatory or patent term extension;

E. An Order that the effective date of any FDA approval of ANDA No. 78-356 and/or ANDA No. 78-357 be no earlier than the date on which the '683 patent expires, including any regulatory or patent term extension;

F. An Order that the effective date of any FDA approval of ANDA No. 78-356 and/or ANDA No. 78-357 be no earlier than the date on which the '684 patent expires, including any regulatory or patent term extension;

G. Preliminary and permanent injunctions enjoining Defendants and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, importing, offering to sell, or selling Orchid's Proposed Products until after the expiration of the '582 patent, including any regulatory or patent term extension;

H. Preliminary and permanent injunctions enjoining Defendants and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, importing, offering to sell, or selling Orchid's Proposed Products until after the expiration of the '683 patent, including any regulatory or patent term extension;

I. Preliminary and permanent injunctions enjoining Defendants and their officers, agents, attorneys and employees, and those acting in privity or concert with them, from making, using, importing, offering to sell, or selling Orchid's Proposed Products until after the expiration of the '684 patent, including any regulatory or patent term extension;

J. A declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Orchid's Proposed Products will directly infringe or induce and/or contribute to infringement of the '582 patent;

K. A declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Orchid's Proposed Products will directly infringe or induce and/or contribute to infringement of the '683 patent;

L. A declaration that the commercial manufacture, use, importation into the United States, sale or offering for sale of Orchid's Proposed Products will directly infringe or induce and/or contribute to infringement of the '684 patent;

M. If Defendants engage in the commercial manufacture, use, importation into the United States, offer to sell, or sale of Orchid's Proposed Products prior to the expiration of the '582 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed based on the willfulness of the infringement, together with interest;

N. If Defendants engage in the commercial manufacture, use, importation into the United States, offer to sell, or sale of Orchid's Proposed Products prior to the expiration of the '683 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed based on the willfulness of the infringement, together with interest;

O. If Defendants engage in the commercial manufacture, use, importation into the United States, offer to sell, or sale of Orchid's Proposed Products prior to the expiration of the '684 patent, a Judgment awarding damages to Plaintiffs resulting from such infringement, increased to treble the amount found or assessed based on the willfulness of the infringement, together with interest;

P. Attorneys' fees in this action based on willful infringement pursuant to 35 U.S.C. § 284 and/or as an exceptional case pursuant to 35 U.S.C. §§ 271(e)(4) and 285;

Q. Costs and expenses in this action; and

R. Such further and other relief as this Court may deem just and proper.

Dated: September 26, 2007

Respectfully submitted,

s/ Charles M. Lizza

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LOCAL CIVIL RULE 11.2 & 40.1 CERTIFICATION

I hereby certify that the matters captioned: (1) *Schering Corporation v. Zydus Pharmaceuticals, USA, Inc., et al.*, Civil Action No. 06-4715 (MLC) (D.N.J.); (2) *Schering Corporation v. Caraco Pharmaceutical Laboratories Ltd., et al.*, Civil Action No. 06-14386 (E.D. Mich.); and (3) *Schering Corporation v. GeoPharma Inc., et al.*, Civil Action No. 06-1843 (M.D. Fla.), which have been consolidated before the Honorable Mary L. Cooper under the caption, *In Re: Desloratadine Patent Litigation*, MDL No. 1851 (MLC) (D.N.J.), are related patent infringement cases because the defendants in the matter in controversy are defendants in the previously identified matters, and the alleged acts causing the infringement in both cases are the same, *i.e.*, based upon the defendants' filing of the same ANDAs with the FDA. Also, the patents asserted in the current matter are related to the previously identified matters because all the patents are associated with Clarinex® products.

I also certify that the matters captioned, *Sepracor Inc., et al. v. Glenmark Pharmaceuticals, Ltd., et al.*, Civil Action No. 07-3385 (SRC) (D.N.J.) and *Sepracor Inc., et al. v. Sun Pharmaceutical Industries Ltd., et al.*, Civil Action No. 07-4213 (JAP) (D.N.J.), are related actions because they involve the same plaintiffs and the same patents as the matter in controversy.

In light of the number of related cases pending before different judges, I submitted a letter to the Honorable Garrett E. Brown, Chief Judge of this Court, on September 19, 2007, to request that the related cases, including the current matter, be reassigned to Judge Cooper, before whom the earlier filed, related cases are pending. As stated in my letter, reassigning these cases will avoid a situation where many different judges could be separately presiding over each one of

the several related cases, in turn, impacting judicial resources and possibly resulting in inconsistent rulings.

I further certify that, to the best of my knowledge, the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding.

Dated: September 26, 2007

By: *s/ Charles M. Lizza*

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EXHIBIT 18

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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

SEPRACOR INC. and UNIVERSITY OF MASSACHUSETTS	)	
Plaintiffs,	)	Hon. Mary L. Cooper Case No. 07-CV-4623 (MLC) (TJB)
v.	)	
ORCHID CHEMICALS & PHARMACEUTICALS LTD., ORCHID HEALTHCARE, and ORGENUS PHARMA, INC.,	)	**DEFENDANTS' ANSWER, AFFIRMATIVE DEFENSES AND COUNTERCLAIM**
Defendants.	)	

Defendants Orchid Chemicals & Pharmaceuticals Ltd., Orchid Healthcare and Orgenus Pharma, Inc. (collectively "Defendants"), by and through their attorneys, hereby jointly respond to the complaint of plaintiffs Sepracor Inc. and University of Massachusetts (collectively "Plaintiffs"), as follows:

Nature of the Action

1. Defendants are without information or knowledge sufficient to admit or deny whether United States Patent Nos. 7,211,582 (the "582 Patent"), 7,214,683 (the "683 Patent") and 7,214,684 (the "684 Patent") are owned by Defendants, and therefore deny those allegations and the remaining allegations of paragraph 1 of the complaint.

The Parties

2. Defendants are without information or knowledge sufficient to admit or deny the allegations of paragraph 2, and therefore deny those allegations.

3. Defendants are without information or knowledge sufficient to admit or deny the allegations of paragraph 3, and therefore deny those allegations.

4. Defendants admit the allegations of paragraph 4.

5. Defendants admit that Defendant Orchid Healthcare is a division of Orchid Chemicals & Pharmaceuticals Ltd., having a place of business at Plot No. B3-B6 & B11-B14, Sipcot Industrial Park, Irungattukottai, Sriperumbudur (TK) – 602 105, Kancheepuram District, Tamil Nadu, India, but deny the remaining allegations of paragraph 5.

6. Defendants admit that Defendant Orgenus Pharma, Inc. is a New Jersey Corporation having a place of business at 116 Village Boulevard, Suite 200, Princeton, New Jersey, 08540, but deny the remaining allegations of paragraph 6.

7. Defendants admit that the complaint refers to Orchid Chemicals & Pharmaceuticals, Ltd. and Orchid Healthcare collectively as Orchid, as stated in paragraph 7.

8. Defendants admit that Orchid is in the business of manufacturing generic pharmaceutical products, but deny the remaining allegations of paragraph 8.

9. Defendants admit that they filed with the FDA, pursuant to 21 U.S.C. §355(j), ANDA No. 78-356 concerning a generic drug in competition with Desloratadine Orally Disintegrating Tablets, 2.5 mg and 5 mg, which Schering Corporation markets under the brand name Clarinex®, and ANDA No. 78-357 concerning a generic drug in competition with Desloratadine Tablets, 5 mg, which Schering Corporation markets under the brand name Clarinex®, but deny the remaining allegations of paragraph 9.

10. Defendants admit that they are seeking FDA approval to market generic products in the United States, but deny the remaining allegations of paragraph 10.

Jurisdiction and Venue

11. Defendants admit the allegations of paragraph 11.

12. Defendants admit the allegations of paragraph 12.

13. Defendants admit that this court has personal jurisdiction over Orchid and that Orchid markets and sells generic drugs throughout the United States and in this judicial district, but deny the remaining allegations of paragraph 13.

14. Defendants admit that this court has personal jurisdiction over Orchid and that Orchid is a defendant and has filed certain counterclaims in *Schering Corporation v. Zydus Pharmaceuticals, USA, Inc. et al.*, D.N.J., Civil Action No. 3:06-4715 (MLC) (TJB), but deny the remaining allegations of paragraph 14.

15. Defendants admit the allegations of paragraph 15.

The Patents in Suit and the Clarinex® Drug Products

16. Defendants admit that a copy of the 582 Patent having an issue date of May 1, 2007, is attached as Exhibit A to the complaint; are without information or knowledge sufficient to admit or deny whether Plaintiffs are the assignees of the entire right, title and interest in the 582 Patent, and therefore deny those allegations; and deny the remaining allegations of paragraph 16.

17. Defendants admit that a copy of the 683 Patent having an issue date of May 8, 2007, is attached as Exhibit B to the complaint; are without information or knowledge sufficient to admit or deny whether Plaintiffs are the assignees of the entire right, title and interest in the 683 Patent, and therefore deny those allegations; and deny the remaining allegations of paragraph 17.

18. Defendants admit that a copy of the 684 Patent having an issue date of May 8, 2007 is attached as Exhibit C to the complaint; are without information or knowledge sufficient to admit or deny whether Plaintiffs are the assignees of the entire right, title and interest in the 684 Patent, and therefore deny those allegations; and deny the remaining allegations of paragraph 18.

19. Defendants admit that the 582, 683 and 684 Patents are identified in the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") in association with 5 milligram Desloratadine Tablets, which are sold as a commercial product under the trade name Clarinex®, and 2.5 and 5 milligram Desloratadine Orally Disintegrating Tablets, which are sold as a commercial product under the trade name Clarinex® RediTabs®, but deny the remaining allegations of paragraph 19.

Acts Giving Rise to this Action

20. Defendants admit that Plaintiffs Sepracor Inc. ("Sepracor") and University of Massachusetts ("UMass") received a letter from Orchid, dated August 13, 2007, notifying them that Orchid had filed with the FDA, pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)), ANDA No. 78-356 to obtain approval to engage in the commercial manufacture, use, or sale of a generic drug in competition with Desloratadine Orally Disintegrating Tablets, 2.5 mg and 5 mg, which Schering Corporation markets under the brand name Clarinex®, but deny the remaining allegations of paragraph 20.

21. Defendants admit that Plaintiffs Sepracor and UMass received a second letter from Orchid, dated August 13, 2007, notifying them that Orchid had filed with the FDA, pursuant to 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355(j)), ANDA No. 78-357 to obtain approval to engage in the commercial manufacture, use, or sale of a generic drug in competition with Desloratadine Tablets, 5 mg, which Schering Corporation markets under the brand name Clarinex®, but deny the remaining allegations of paragraph 21.

22. Defendants admit that they are seeking FDA approval to engage in the commercial manufacture, use, or sale of a generic drug in competition with Desloratadine Orally Disintegrating Tablets, 2.5 mg and 5 mg, which Schering Corporation markets under the brand name Clarinex®, and to engage in the commercial manufacture, use, or sale of a generic drug in competition with Desloratadine Tablets, 5 mg, which Schering Corporation markets under the brand name Clarinex®, but deny the remaining allegations of paragraph 22.

23. Defendants admit the allegations of paragraph 23.

24. Defendants deny the allegations of paragraph 24.

25. Defendants admit that ANDA No. 78-356 concerns a generic drug in competition with Desloratadine Orally Disintegrating Tablets, 2.5 mg and 5 mg, which Schering Corporation markets under the brand name Clarinex®, and ANDA No. 78-357 concerns a generic drug in competition with Desloratadine Tablets, 5 mg, which Schering Corporation markets under the brand name Clarinex®, but deny the remaining allegations of paragraph 25.

26. Defendants need not respond to the allegations of paragraph 26 which purport to state conclusions of law as to which no response is necessary.

Count I

27. Defendants repeat their answers to the allegations of paragraphs 1 through 26 of the complaint as if fully set forth at length here.

28. Defendants deny the allegations of paragraph 28.

29. Defendants deny the allegations of paragraph 29.

30. Defendants deny the allegations of paragraph 30.

31. Defendants deny the allegations of paragraph 31.

32. Defendants deny the allegations of paragraph 32.

Count II

33. Defendants repeat their answers to the allegations of paragraphs 1 through 32 of the complaint as if fully set forth at length here.

34. Defendants deny the allegations of paragraph 34.

35. Defendants deny the allegations of paragraph 35.

36. Defendants deny the allegations of paragraph 36.

37. Defendants deny the allegations of paragraph 37.

38. Defendants deny the allegations of paragraph 38.

Count III

39. Defendants repeat their answers to the allegations of paragraphs 1 through 38 of the complaint as if fully set forth at length here.

40. Defendants deny the allegations of paragraph 40.

41. Defendants deny the allegations of paragraph 41.

42. Defendants deny the allegations of paragraph 42.

43. Defendants deny the allegations of paragraph 43.

44. Defendants deny the allegations of paragraph 44.

First Affirmative Defense

The complaint fails to state a claim upon which relief can be granted.

Second Affirmative Defense

One or more claims of the 582, 683 and 684 patents are invalid for failing to satisfy one or more requirements of Title 35 of the United States Code, including but not limited to 35 U.S.C. §§102, 103, and/or 112.

Third Affirmative Defense

Defendants do not infringe, have not infringed, are not inducing, contributing to, or cooperating in the infringement of, and have not induced, contributed to, or cooperated in the infringement of, the 582, 683 and 684 patents.

Fourth Affirmative Defense

The complaint should be dismissed because the 582, 683 and 684 patents are not properly listed in the Orange Book.

WHEREFORE, Defendants Orchid Chemicals & Pharmaceuticals Ltd., Orchid Healthcare, and Orgenus Pharma, Inc. demand judgment in their favor, dismissing the complaint

with prejudice, together with costs of suit, and such other and further relief as the Court may deem just and appropriate.

Counterclaim

Defendants/counterclaimants Orchid Chemicals & Pharmaceuticals Ltd., Orchid Healthcare, and Orgenus Pharma, Inc., as and for their counterclaim against Plaintiffs, state and allege as follows:

Nature of the Action

1. This counterclaim seeks a declaratory judgment of non-infringement and invalidity of the 582, 683 and 684 Patents asserted by Plaintiffs in this action. Defendants seek judgment under the patent laws of the United States, 35 U.S.C. § 101, *et seq.*, and the Declaratory Judgment Act, 28 U.S.C. § 2201 and 2202.

The Parties

2. Defendant/counterclaimant Orchid Chemicals & Pharmaceuticals Ltd. is a public limited liability company organized under the laws of India, which maintains its principal place of business at Orchid Towers, No. 313, Valluvar Kottam Road, Nungambakkam, Chennai – 600 034, Tamil Nadu, India.

3. Defendant/counterclaimant Orchid Healthcare is an unincorporated division of Orchid Chemicals & Pharmaceuticals Ltd., which maintains a place of business at Plot Nos. B3-B6 and B11-B-14, SIPCOT Industrial Park, Irungattukottai, Kancheepuram District – 602 105, India.

4. Defendant/counterclaimant Orgenus Pharma Inc. is a corporation organized under the laws of New Jersey and maintains its principal place of business at 116 Village Boulevard, Suite 200, Princeton, New Jersey 08540.

5. Plaintiff Sepracor Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 84 Waterford Drive, Marlborough, Massachusetts 01752.

6. Plaintiff University of Massachusetts is a public institution of higher education of the Commonwealth of Massachusetts, having a place of business at 55 Lake Avenue North, Worcester, Massachusetts 01655.

Jurisdiction and Venue

7. This Court has subject matter jurisdiction over this amended counterclaim pursuant to 28 U.S.C. §§ 1331 and 1338(a), and the Declaratory Judgment Act, 28 U.S.C. §§ 2201 and 2202. An actual, justiciable controversy exists within this jurisdiction regarding, *inter alia,* the validity of the 582, 683 and 684 patents and the technical act of infringement of Defendants-counterclaimants' generic drugs that would compete with Desloratadine Orally Disintegrating Tablets, 2.5 mg and 5 mg, and Desloratadine Tablets, 5 mg, as evidenced by the filing of Plaintiffs' complaint and Plaintiffs' listing of the 582, 683 and 684 patents in the Orange Book in association with 5 milligram Desloratadine Tablets and 2.5 and 5 milligram Desloratadine Orally Disintegrating Tablets.

8. Venue is proper in this judicial district pursuant to 28 U.S.C. § 1391(d).

COUNT I
(Non-Infringement)

9. Defendants/counterclaimants do not infringe and have not infringed the 582, 683 or 684 patents directly, contributorily or by inducement.

COUNT II
(Invalidity)

10. One or more of the claims of the 582, 683 and 684 patents are invalid because they fail to satisfy one or more of the conditions for patentability under Title 35 of the United States Code, including one or more of the following: 35 U.S.C. §§102, 103, and/or 112.

WHEREFORE, Defendants/counterclaimants respectfully pray for judgment:

a. Declaring the 582, 683 and 684 patents invalid and/or not infringed by Defendants-counterclaimants;

b. Awarding Defendants-counterclaimants such other and further relief as the Court may deem just and appropriate.

Dated: December 31, 2007

s/ Bradley L. Mitchell
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CERTIFICATE OF SERVICE

I hereby certify that the foregoing Defendants' Answer, Affirmative Defenses And Counterclaim was served on this 31st day of December, 2007, on the following by means of the Court's Notice of Electronic Filing:

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EXHIBIT 19

ORIGINAL

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF NEW YORK

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., MERZ PHARMA GMBH & CO. KGAA, and MERZ PHARMACEUTICALS GMBH,

Plaintiffs,

vs.

GENPHARM, L.P., GENPHARM INC., INTERPHARM, INC., and INTERPHARM HOLDINGS, INC.,

Defendants.

CV 08 444

GERSHON, J.

Civil Action No. _____

REYES, M.J.

FILED
IN CLERK'S OFFICE
U.S. DISTRICT COURT E.D.N.Y.
★ JAN 31 2008 ★
BROOKLYN OFFICE

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COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for their Complaint against Defendants Genpharm, L.P., Genpharm Inc., Interpharm, Inc., and Interpharm Holdings, Inc. (collectively "Defendants") hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Genpharm, L.P. ("Genpharm LP") is a New York entity, and the sister company and agent of Genpharm Inc., having a principal place of business at 150 Motor Parkway, Hauppauge, New York 11788. Upon information and belief, Defendant Genpharm LP manufactures and/or distributes numerous generic drugs for sale and use throughout the United States, including in this judicial district.

6. Upon information and belief, Defendant Genpharm Inc. ("Genpharm") is a Canadian corporation having a principal place of business at 85 Advance Road, Etobicoke, Ontario M8Z 2S6, Canada. Upon information and belief, Defendant Genpharm, itself and through its sister company and agent Defendant Genpharm LP, manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

7. Upon information and belief, Defendant Interpharm, Inc. ("Interpharm") is a New York corporation, and the subsidiary and agent of Interpharm Holdings, Inc., having a principal place of business at 75 Adams Avenue, Hauppauge, New York 11788. Upon information and belief, Defendant Interpharm, itself and on behalf of its parent and principal Defendant Interpharm Holdings, manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

8. Upon information and belief, Defendant Interpharm Holdings, Inc. ("Interpharm Holdings") is a Delaware corporation having a principal place of business at 75 Adams Avenue, Hauppauge, New York 11788. Upon information and belief, Defendant Interpharm Holdings, itself and through its subsidiary and agent Defendant Interpharm, manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

9. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

JURISDICTION AND VENUE

10. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

11. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Labs, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

12. This Court has personal jurisdiction over Defendant Genpharm LP by virtue of the fact that, *inter alia*, Genpharm is a New York corporation.

13. This Court has personal jurisdiction over Defendant Genpharm by virtue of, *inter alia*: (1) its presence in New York through its sister company and agent Genpharm LP; and (2) its systematic and continuous contacts with New York, including through its sister company and agent Genpharm LP.

14. This Court has personal jurisdiction over Defendant Interpharm by virtue of the fact that, *inter alia*, Interpharm is a New York corporation.

15. This Court has personal jurisdiction over Defendant Interpharm Holdings by virtue of, *inter alia*: (1) its presence in New York at its principal place of business; (2) its presence in New York through its subsidiary and agent Interpharm; and (3) its systematic and continuous contacts with New York, including through its subsidiary and agent Interpharm.

16. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

17. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

18. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

19. Forest is the exclusive distributor of Namenda® in the United States.

24. Genpharm LP is jointly and severally liable for any infringement of the '703 patent. Upon information and belief, Genpharm LP participated in, contributed to, aided, abetted and/or induced Genpharm's submission of ANDA No. 90-050 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

25. Genpharm LP's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 90-050 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Genpharm LP commercially manufactures, uses, offers to sell, sells, or imports any of the Genpharm Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

26. Genpharm and Genpharm LP were aware of the '703 patent prior to filing ANDA No. 90-050.

27. Genpharm's and Genpharm LP's actions render this an exceptional case under 35 U.S.C. § 285.

28. Plaintiffs will be irreparably harmed by Genpharm's and Genpharm LP's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

29. Plaintiffs have sought to enjoin Genpharm's and Genpharm LP's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 25, 2008, Civil Action No. 1:08-CV-00052. Genpharm and Genpharm LP are properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and

belief, Plaintiffs understand that Genpharm and Genpharm LP may nevertheless contest jurisdiction in that venue. Given the possible consequences if Genpharm and Genpharm LP succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Genpharm and Genpharm LP are unsuccessful in any such challenge, Plaintiffs will dismiss this action.

Count II – Infringement Of The '703 Patent By Defendants Interpharm And Interpharm Holdings

30. Upon information and belief, Defendant Interpharm, on behalf of its parent and principal Interpharm Holdings, submitted ANDA No. 90-041 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Interpharm Generic Products"). ANDA No. 90-041 specifically seeks FDA approval to market the Interpharm Generic Products prior to the expiration of the '703 patent.

31. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Interpharm alleged in ANDA No. 90-041 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Interpharm Generic Products. Plaintiffs received written notification of ANDA No. 90-041 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 19, 2007.

32. Interpharm's submission of ANDA No. 90-041 to the FDA, on behalf of its parent and principal Interpharm Holdings, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Interpharm commercially manufactures, uses, offers to sell, sells, or imports any of the

Interpharm Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

33. Interpharm Holdings is jointly and severally liable for any infringement of the '703 patent. Upon information and belief, Interpharm Holdings participated in, contributed to, aided, abetted and/or induced Interpharm's submission of ANDA No. 90-041 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

34. Interpharm Holdings' participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 90-041 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Interpharm Holdings commercially manufactures, uses, offers to sell, sells, or imports any of the Interpharm Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

35. Interpharm and Interpharm Holdings were aware of the '703 patent prior to filing ANDA No. 90-041.

36. Interpharm's and Interpharm Holdings' actions render this an exceptional case under 35 U.S.C. § 285.

37. Plaintiffs will be irreparably harmed by Interpharm's and Interpharm Holdings' infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

38. Plaintiffs have sought to enjoin Interpharm's and Interpharm Holdings' infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 25, 2008, Civil Action No. 1:08-CV-00052. Interpharm and Interpharm Holdings are properly subject to

personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs understand that Interpharm and Interpharm Holdings may nevertheless contest jurisdiction in that venue. Given the possible consequences if Interpharm and Interpharm Holdings succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Interpharm and Interpharm Holdings are unsuccessful in any such challenge, Plaintiffs will dismiss this action.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That all Defendants have infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendants' respective ANDAs identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: January 31, 2008

Respectfully submitted,

KIRKLAND & ELLIS LLP

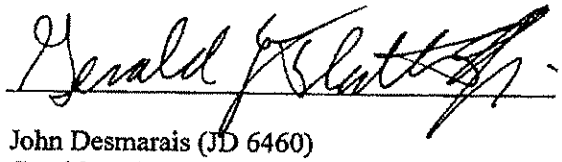

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EXHIBIT A

United States Patent [19]

Bormann et al.

[11] **Patent Number: 5,061,703**

[45] **Date of Patent: Oct. 29, 1991**

[54] **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

[75] Inventors: **Joachim Bormann**, Frankfurt; **Markus R. Gold**, Nauheim; **Wolfgang Schatton**, Eschborn, all of Fed. Rep. of Germany

[73] Assignee: **Merz + Co. GmbH & Co.**, Frankfurt am Main, Fed. Rep. of Germany

[21] Appl. No.: **508,109**

[22] Filed: **Apr. 11, 1990**

[30] **Foreign Application Priority Data**

Apr. 14, 1989 [EP] European Pat. Off. 89106657

[51] Int. Cl.[5] A61K 31/13; A61K 31/41; A61K 31/55; A61K 31/445

[52] U.S. Cl. 514/212; 514/325; 514/359; 514/662

[58] Field of Search 514/212, 325, 359, 662

[56] **References Cited**

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0227410 7/1987 European Pat. Off. .

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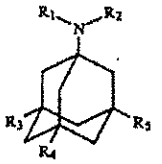
Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula



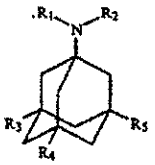
(I)

wherein
R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;
wherein
R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;
wherein
R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,
or a pharmaceutically-acceptable salt thereof, is disclosed.

13 Claims, No Drawings

ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

The present invention relates to a method for the prevention or treatment of cerebral ischemia using an adamantane derivative of the following general formula



(I)

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic radical with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl; and

wherein

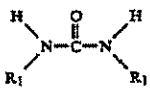
R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group, or a pharmaceutically-acceptable acid addition salt thereof. Herein branched or straight C_1–C_6 alkyl groups representatively include methyl, ethyl, iso- and n-propyl, n-, iso- and t-butyl, n-pentyl, n-hexyl, and the isomers thereof.

Certain 1-amino adamantanes of formula (I) are known. 1-amino-3,5-dimethyl adamantane, for example, is the subject matter of German patents 22 19 256 and 28 56 393.

Some 3,5-disubstituted 1-amino adamantanes of formula (I) are described in U.S. Pat. No. 4,122,193. 1-amino-3-ethyl adamantane is described in German Patent 22 32 735.

The compounds of formula (I) are generally prepared by alkylation of halogenated adamantanes, preferably bromo- or chloroadamantanes. The di- or tri-substituted adamantanes are obtained by additional halogenation and alkylation procedures. The amino group is introduced either by oxidation with chromiumtrioxide and bromination with HBr or bromination with bromine and reaction with formamide followed by hydrolysis. The amino function can be alkylated according to generally-accepted methods. Methylation can, for example, be effected by reaction with chloromethyl formate and subsequent reduction. The ethyl group can be introduced by reduction of the respective acetamide.

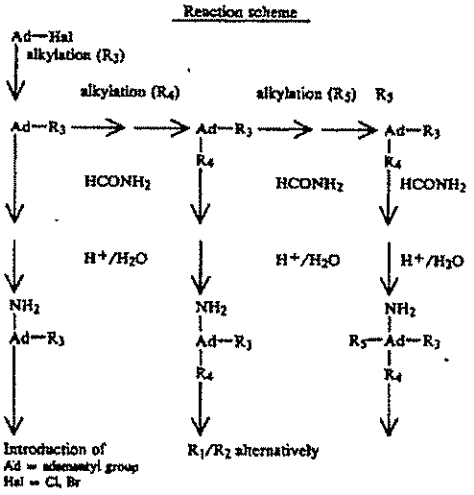
In accordance with U.S. Pat. No. 4,122,193 amination can also be effected by reaction of the respective 1-halogen-3,5- or -7-substituted adamantane with a urea derivative of the formula



wherein R_1 is hydrogen or alkyl.

The compounds according to formula (I) are prepared according to the following reaction scheme:

Reaction scheme



Alkylation of the halogenated adamantanes can be achieved by known methods, for example, through Friedel-Crafts reaction (introduction of phenyl group), or by reaction with vinylidene chloride, subsequent reduction and suitable Wittig reaction of the aldehydes and subsequent hydration, or by introduction of ethylene and subsequent alkylation with appropriate cuprates, or by introduction of ethylene and reduction of the halogen alkyl adamantanes, or by acylation with CO_2 and roduction of the carboxylic acid.

The compounds according to formula (I) known from the above-cited patents have so far been used for the treatment of parkinsonian and parkinsonoid diseases. Their mode of action is attributed to a dopaminergic influence on the CNS, either by an increased release of the transmitter substance dopamine or by an inhibition of its uptake. This compensates the imbalance of the dopamine/acetylcholine system.

In contrast to this type of disease, cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas (Rothmann & Olney, Trends Neurosci 10, 1989, pp. 299).

Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels (Kemp et al., Trends Pharmacol., Sci. 8, 1987, pp. 414).

Such intervention can, for example, be effected using substituted fluoro and hydroxy derivatives of dibenzo-[a,d]-cyclo-heptene-5,10-imine which are described in EP-A 0 264 183.

These heterocyclic, aromatic compounds are lipophilic and exhibit NMDA receptor channel-antagonistic and anticonvulsive properties. They are prepared by a relatively expensive method generating enantiomer mixtures which may be split into the individual optical antipodes.

The present invention is aimed at preparing and employing compounds which can be chemically generated

by simple methods, exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of cerebral ischemia.

This objective can be achieved according to the invention by using the 1-amino adamantanes of formula (I).

It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia. Therefore, the adamantane derivatives of formula (I) are especially suited for the prevention and treatment of cerebral ischemia after apoplexy, open-heart surgery, cardiac standstill, subarachnoidal hemorrhage, transient cerebro-ischemic attacks, perinatal asphyxia, anoxia, hypoglycemia, apnoea and Alzheimer's disease. The amount employed is a cerebral ischemia-alleviating or preventive amount.

Examples of compounds prepared and used according to the invention are:

1-amino adamantane
1-amino-3-phenyl adamantane
1-amino-methyl-adamantane
1-amino-3,5-dimethyl adamantane (test compound no. 1)
1-amino-3-ethyl adamantane (test compound no. 2)
1-amino-3-isopropyl adamantane (test compound no. 3)
1-amino-3-n-butyl adamantane
1-amino-3,5-diethyl adamantane (test compound no. 4)
1-amino-3,5-diisopropyl adamantane
1-amino-3,5-di-n-butyl adamantane
1-amino-3-methyl-5-ethyl adamantane
1-N-methylamino-3,5-dimethyl adamantane (test compound no. 5)
1-N-ethylamino-3,5-dimethyl adamantane (test compound no. 6)
1-N-isopropyl-amino-3,5-dimethyl adamantane
1-N,N-dimethyl-amino-3,5-dimethyl adamantane
1-N-methyl-N-isopropyl-amino-3-methyl-5-ethyl adamantane
1-amino-3-butyl-5-phenyl adamantane
1-amino-3-pentyl adamantane
1-amino-3,5-dipentyl adamantane
1-amino-3-pentyl-5-hexyl adamantane
1-amino-3-pentyl-5-cyclohexyl adamantane
1-amino-3-pentyl-5-phenyl adamantane
1-amino-3-hexyl adamantane
1-amino-3,5-dihexyl adamantane
1-amino-3-hexyl-5-cyclohexyl adamantane
1-amino-3-hexyl-5-phenyl adamantane
1-amino-3-cyclohexyl adamantane (test compound no. 7)
1-amino-3,5-dicyclohexyl adamantane
1-amino-3-cyclohexyl-5-phenyl adamantane
1-amino-3,5-diphenyl adamantane
1-amino-3,5,7-trimethyl adamantane
1-amino-3,5-dimethyl-7-ethyl adamantane (test compound no. 8)
1-amino-3,5-diethyl-7-methyl adamantane
1-N-pyrrolidino and 1-N-piperidine derivatives,
1-amino-3-methyl-5-propyl adamantane
1-amino-3-methyl-5-butyl adamantane
1-amino-3-methyl-5-pentyl adamantane
1-amino-3-methyl-5-hexyl adamantane
1-amino-3-methyl-5-cyclohexyl adamantane
1-amino-3-methyl-5-phenyl adamantane
1-amino-3-ethyl-5-propyl adamantane
1-amino-3-ethyl-5-butyl adamantane
1-amino-3-ethyl-5-pentyl adamantane
1-amino-3-ethyl-5-hexyl adamantane
1-amino-3-ethyl-5-cyclohexyl adamantane
1-amino-3-ethyl-5-phenyl adamantane
1-amino-3-propyl-5-butyl adamantane
1-amino-3-propyl-5-pentyl adamantane
1-amino-3-propyl-5-hexyl adamantane
1-amino-3-propyl-5-cyclohexyl adamantane
1-amino-3-propyl-5-phenyl adamantane
1-amino-3-butyl-5-pentyl adamantane
1-amino-3-butyl-5-hexyl adamantane
1-amino-3-butyl-5-cyclohexyl adamantane

their N-methyl, N,N-dimethyl, N-ethyl, N-propyl derivatives and their acid addition compounds.

Preferred compounds of formula (I) are those wherein R_1 and R_2 are hydrogen such as, for example, 1-amino-3-ethyl-5,7-dimethyl adamantane, and compounds wherein R_1, R_2, R_4 and R_5 are hydrogen such as, for example, 1-amino-3-cyclohexyl adamantane and 1-amino-3-ethyl adamantane.

Additional preferred compounds are those wherein R_1, R_2 and R_5 are hydrogen such as, for example, 1-amino-3-methyl-5-propyl or 5-butyl adamantane, 1-amino-3-methyl-5-hexyl or cyclohexyl adamantane, or 1-amino-3-methyl-5-phenyl adamantane.

Especially preferred compounds are 1-amino-3,5-dimethyl adamantane, 1-amino-3,5-diethyl adamantane, i.e., compounds wherein R_1, R_2 and R_5 are hydrogen, and compounds wherein R_1 and R_5 are hydrogen, R_2 is methyl or ethyl, and R_3 and R_4 are methyl such as, for example, 1-N-methylamino-3,5-dimethyl adamantane and 1-N-ethylamino-3,5-dimethyl adamantane.

The adamantane derivatives of formula (I) may be applied as such or in the form of their pharmaceutically-acceptable acid addition salts including, for example, the hydrochlorides, hydrobromides, sulfates, acetates, succinates or tartrates, or their acid addition salts with fumaric, maleic, citric, or phosphoric acids.

The compounds of formula (I) are administered in suitable form in doses ranging from about 0.01 to 100 mg/kg. Appropriate presentation forms are, for example, combinations of the active substance with common pharmaceutical carriers and adjuvants in the form of tablets, coated tablets, and sterile solutions or suspensions for injection. Pharmaceutically-acceptable carriers are, for example, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, gum arabic, corn starch, or cellulose, combined with diluents such as water, polyethylene glycol, etc. Solid presentation forms are prepared according to common methods and may contain up to 50 mg of the active ingredient per unit.

The efficacy of the compounds of formula (I) is described in the following pharmacological tests.

A. Displacement of TCP Binding

Phencyclidine (PCP), a known NMDA antagonist, binds to the NMDA receptor-associated ionic channel and blocks ionic transport (Garthwaite & Garthwaite, Neurosci. Lett. 83, 1987, 241–246). Additionally, PCP has been shown to prevent the destruction of brain cells after cerebral ischemia in rats (Sauer et al., Neurosci. Lett. 91, 1988, 327–332).

The interaction between compounds of formula (I) and the PCP bond is studied in the following. In this test ^{3}H-TCP, a PCP analogue, is used.

A membrane preparation of rat cortex is incubated with ^{3}H-TCP which is an analogue of phencyclidine (PCP) (Quirion & Pert 1982, Eur. J. Pharmacol. 83:155).

The interaction with the TCP binding is assessed for test compound no. 1 (1-amino-3,5-dimethyl adamantane) in a competitive experiment. This test shows that compound no. 1 is very effective in displacing TCP from the bond. The IC_{50} value is 89 nM. The conclusion can be drawn that compound no. 1 binds to NMDA receptor channels at the same site as the NMDA antagonist PCP.

B. Blocking of NMDA Receptor Channels

In the following test it is shown that the compounds of formula (I) according to the invention are as effective as PCP in blocking the NMDA receptor channel.

In the patch-clamp experiment, the current flowing through NMDA-activated membrane channels of cultivated spinal marrow neurons (mouse) is measured (Hamill et al 1981, Pflügers Arch. 312: 85–100). After application of 20 μM NMDA, the current signal of the cell is integrated for 20 sec. and recorded as a control answer (A_c). During succeeding application of 20 μM NMDA and 6 μM of an adamantane derivative, the intensity of the substance effect can be determined as a relative change of the control answer ($A/A_c - A$ = test answer).

The results are summarized in the following Table 1:

TABLE 1

Compound no.	1-A/Ac	n
1	0.66 ± 0.05	14
2	0.44 ± 0.08	7
3	0.58 ± 0.07	7
4	0.50 ± 0.11	5
5	0.56 ± 0.07	7
6	0.38 ± 0.05	7
7	0.25 ± 0.04	11
8	0.50 ± 0.03	6
PCP	0.50 ± 0.04	7
MK-801	0.60 ± 0.05	22

The values are given as means ± SEM.

As can be seen from the results, the aminoadamantane derivatives of formula (I) are able to block the NMDA receptor channel as has been described for PCP (Bertolini et al., Neurosci. Lett. 84, 1988, 351–355) and for 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5,10-imine (MK-801) (EP-A 0 264 183).

C. Anticonvulsive Effect

4, 12, 36, 108 and 324 mg/kg of the test substance is administered to mice by the intraperitoneal route (5 animals per dose). The supermaximum electroshock test is applied forty (40) minutes after application of the substance to investigate the anti-convulsive potential of the substance. The protected animals are added up over all dosages (score; maximum=25 animals).

The results are given in the following Table 2.

TABLE 2

Compound no.	Anticonvulsive action (score)	Mean	ED_{50} (mg/kg)
1	18		
	16		
	16		
	15	16.3	16
2	15		
	14		
	12	13.7	30
4	16		
	16		
	11	14.3	24
5	17		
	17	17.0	13
Standards:			
PCP	19	19.0	9
MK-801	25	25.0	<1

The ED_{50} values were estimated according to Litchfield, J. T. and Wilcoxon, F., J. Pharmacol. Exp. Therap. 96, 99–113 (1949).

As can be seen from the above results, aminoadamantane derivatives of formula (I) exhibit a protective effect against electrically induced convulsions. They therefore have an anticonvulsive effect.

D. Correlation Between Channel-Blocking and Anticonvulsive Action

The correlation between the action of the tested adamantane derivatives 1–8 at the NMDA receptor channel (in vitro) and the anticonvulsive effect (in vivo) has been tested. For this purpose an xy diagram of both test parameters is plotted. It shows that there is a correlation between the blocking of the NMDA receptor channel and the anticonvulsive action of the adamantanes of formula (I).

E. Protection Against Cerebral Ischemia

Both carotid arteries are occluded in rats for 10 minutes. At the same time the blood pressure is reduced to 60–80 mg Hg by withdrawal of blood (Smith et al. 1984, Acta Neurol. Scand. 69: 385, 401). The ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood. After seven days the brains of the test animals are histologically examined for cellular changes in the CA1–CA4 region of the hippocampus, and the percentage of destroyed neurons is determined. The action of test compound No. 1 is determined after a single administration of 5 mg/kg and 20 mg/kg one (1) hour prior to the ischemia.

The results are summarized in the following Table 3:

TABLE 3

		Test compound no. 1	
Area	Control	5 mg/kg (n = 5)	20 mg/kg (n = 6)
CA1	80.2 ± 1.5	83.0 ± 2.2	53.1 ± 6.1**
CA3	3.6 ± 1.1	7.3 ± 1.8	2.7 ± 1.0
CA4	1.4 ± 0.4	3.7 ± 1.7	0.6 ± 0.3

The values are given in percent of damaged neurons ± SEM.
Significance of the mean difference: **p < 0.01 (U test)

The results show that the reduction of the post-ischemic neuronal brain damage in the CA1 region of the rat hippocampus is statistically significant after the pre-ischemic application of 20 mg/kg of test compound no. 1. Physiological parameters (e.g. blood pressure, body temperature) are not affected by the treatment. Moreover, the results show that the compounds according to formula (I) exhibit a neuroprotective action in cerebral ischemia.

Essentially the same result is attained by employing the compounds of the other Examples, especially those designated test compounds 2–8.

F. Protection Against NMDA-Induced Mortality

It is well known that, subsequent to cerebral ischemia, glutamate and aspartate levels increase massively in the brain. These excitatory aminoacids overstimulate

the NMDA-subtype of the glutamate receptor thus leading to delayed neuronal death. A similar pathophysiological situation is obtained when mice are administered intraperitoneally with 200 mg/kg NMDA. This high dose will eventually cause 100% mortality in the animals (Leander et al. 1984, Brain Res. 448; 115–120). We have found that the adamantane derivatives of the present invention are protective against the NMDA-induced mortality.

Compound No.	Dose mg/kg	Protected Animals
1	50	8/8
	25	6/8
	10	3/8
3	50	6/8
	25	4/8
4	50	7/8
	25	5/8
5	25	5/8

In the control animals, to which no adamantane was administered, the mortality was eight (8) animals out of eight (8).

G. Displacement of [^{3}H] MK-801 Binding in Human Brain Tissue

MK-801 binds to the ion channel associated with the NMDA receptor, as well as TCP does. This binding site is thought to mediate the neuroprotective effects of non-competitive NMDA-antagonists.

We have investigated whether the adamantane derivatives of the present invention are active at the MK-801 binding site. Tissue from frontal cortex was taken from patients at autopsy and homogenates were prepared. Inhibition of specific [^{3}H] MK-801 binding (3 nM) by the test compounds was determined (see e.g. Kornhuber et al. 1989, Eur. J. Pharmacol. 166; 589–590).

The test compounds were highly potent in displacing MK-801 binding, thus indicating a specific interaction with the NMDA receptor channel and predicting neuroprotective properties.

Compound No.	Ki nM
1	536
3	598
4	189
5	1607

wherein K_i is the inhibition constant and nM is nanomoles per liter. Mean values from triplicate experiments are given ± S.E.M.

The inhibition constant Ki is approximately equal to the concentration of the adamantane in nM required to displace 50% of the MK-801 specifically bound to the receptor. In this regard, memantine (Compound No. 1) was found to be the most potent compound subjected to this test, when compared with thirteen (13) other clinically-used and centrally-acting drugs, as reported in the foregoing publication.

The invention is further described by the following illustrative examples, which are not to be construed as limiting:

EXAMPLE 1

Injectable Solution

For preparing a 0.5% solution, dissolve 0.5% active ingredient and 0.8% sodium chloride (DAB 9) in doubly distilled water. Filter the solution through an antimicrobial filter, fill into 2-ml ampoules and sterilize for 20 minutes at 120° C. in an autoclave.

EXAMPLE 2

Solution

Dissolve 1% of active agent in demineralized water. Filter the solution before filling.

EXAMPLE 3

Tablets

1 tablet contains:	
Active ingredient	10.0 mg
Lactose	67.5 mg
Microcrystalline cellulose	18.0 mg
Talc	4.5 mg
	100.0 mg

The substances are mixed and the mixture compressed into 100-mg tablets in a direct tableting procedure without granulation.

EXAMPLE 4

Coated Tablets

Prepare 6-mm tablet cores of 100 mg as described under "Tablets". Coat the tablets in a sugar-coating process by coating the core with a sugar suspension first, followed by staining with a colored syrup and polishing.

The tablet coating consists of:

Sugar	65.0 mg
Talc	39.0 mg
Calcium carbonate	13.0 mg
Gum arabic	6.5 mg
Corn starch	3.7 mg
Shellac	1.1 mg
Polyethylene glycol 6000	0.2 mg
Magnesia usta	1.3 mg
Dye	0.2 mg
	130.0 mg

Total tablet weight: 230 mg

EXAMPLE 5

For preparing a 0.01% infusion solution, dissolve 0.01% of active ingredient and 5% levulose in doubly-distilled water. Filter the solution through an antimicrobial filter, fill into 500-ml infusion bottles, and sterilize.

The example provides 50 mg of active substance per single dose.

EXAMPLE 6

Synthesis of 1-Amino-3-isopropyl Adamantane Hydrochloride (Test Compound No. 3)

A. Preparation of Adamantane Methyl Carboxylate (I)

Stir 1.0 mol of adamantane carboxylic acid in 600 ml of methanol. Under ice cooling, drop 1.53 mol of acetyl chloride into the solution within 1 h. Remove the ice bath, and allow the reaction mixture to reach room temperature. Subsequently, heat for 3 hrs under reflux. Evaporate the reaction mixture to dryness under vacuum and distill. (Yield: 97%).

B. Preparation of Isopropyl Adamantane (II)

Introduce 0.5 mol of magnesium chips into 50 ml of absolute ether, and drop 0.5 mol of methyl iodide into the solution under moisture-free conditions until the ether boils. Subsequently, heat in a water bath until the magnesium has completely dissolved. Into this solution at room temperature drop 0.2 mol of adamantane methyl carboxylate in absolute ether. Then heat to reflux for 3 hours. After cooling, hydrolize with ice and mix with ammonium chloride solution until the precipitate has dissolved. Separate the ether phase, wash the aqueous phase with 2 portions of ether, and wash the combined organic phases with sodium bicarbonate solution. Then dry and evaporate to dryness under vacuum. (Yield: 93%).

C. Preparation of Isopropene Adamantane (III)

Stir 0.25 mol of isopropyl adamantane (II) in 500 ml acetic anhydride for 12 hours at 160° C. Subsequently, pour the reaction mixture onto 1 liter of ice water and extract with ether. Dry the combined organic phases with magnesium sulfate, filter, and evaporate to dryness under vacuum. Distill the residue under vacuum. (Yield: 66%).

D. Preparation of Isopropyl Adamantane (IV)

Dissolve 0.074 mol of adamantyl isopropene (III) in 100 ml of absolute ethanol. Add 4 g of palladium (5% on activated carbon) and hydrate under stirring for 24 hrs at room temperature. Subsequently, filter off the catalyst, and remove the solvent under vacuum. (Yield: 91%).

E. Preparation of 1-Bromo-3-isopropyl Adamantane (V)

Mix 0.034 mol of isopropyl adamantane (IV) with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 h. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until the aqueous solution has discolored. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

F. Preparation of 1-N-formyl-3-isopropyl Adamantane (VI)

Heat 0.028 mol of 1-bromo-3-isopropyl adamantane (V) with 40 ml of formamide to reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

G. Preparation of 1-Amino-3-isopropyl Adamantane Hydrochloride

Mix 0.023 mol of 1-N-formyl-3-isopropyl adamantane (VI) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

EXAMPLE 7

Synthesis of 1-Amino-3-cyclohexyl Adamantane Hydrochloride (Test Compound No. 7)

A. Preparation of 1-Phenyl Adamantane (I)

Heat 0.068 mol of iron(III) chloride to boiling in 20 ml of absolute benzene. Drop 0.0186 mol of 1-bromoadamantane, dissolved in 30 ml of absolute benzene, to the solution. Then heat to boiling for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract the aqueous phase with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 80%).

B. Preparation of 1-Hydroxy-3-phenyl Adamantane (II)

To a solution of 0.03 mol chromiumtrioxide in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-phenyl adamantane at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture onto water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolize the residue with 20 ml of 2N NaOH and 50 ml of methanol. Subsequently, remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629–35.

C. Preparation of 1-Bromo-3-phenyl Adamantane (III)

Stir 0.03 mol of 3-phenyl adamantanol (II) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and 30 min at room temperature. Subsequently, dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

D. Preparation of 1-N-formyl-3-phenyl Adamantane (IV)

Heat 0.03 mol of 1-bromo-3-phenyl adamantane (III) with 50 ml of formamide for 12 hrs to reflux. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 80%).

E. Preparation of 1-Amino-3-phenyl Adamantane Hydrochloride (V)

Heat 0.02 mol of 1-N-formyl-3-phenyl adamantane (IV) with 100 ml of 15% hydrochloric acid at reflux for 24 hours. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

F. Preparation of 1-Amino-3-cyclohexyl Adamantane (VI)

Dissolve 0.011 mol of 1-amino-3-phenyl adamantane (V) in 150 ml glacial acetic acid, mix with 0.3 g of platinum oxide (1% on activated carbon) and hydrate in a

Parr apparatus at 35° C. at a hydrogen pressure of 3 bar. Subsequently, remove the catalyst by filtration and evaporate the filtrate to dryness. Take up the residue in methanol and precipitate the product with ether. Suck off and dry. (Yield: 70%).

EXAMPLE 8

Synthesis of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (Test Compound No. 8)

A. Preparation of 1-Bromo-3,5-dimethyl Adamantane (I)

Mix 0.5 mol of 1,3-dimethyl adamantane with a ten times excess of bromine (5 mol). Slowly heat and stir for 4 hrs under reflux. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

B. Preparation of 1-(2-Bromoethyl)-3,5-dimethyl Adamantane (II)

Mix 1.4 mol of 1-bromo-3,5-dimethyl adamantane (I) in hexane with 0.6 mol of aluminum bromide at −75° C. Subsequently, pass ethylene through the solution for 20–30 minutes, stir for 5 min., and pour the reaction mixture onto ice water. Extract with ether, dry the organic phase and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 48%).

C. Preparation of 1,3-Dimethyl-5-ethyl Adamantane (III)

Dissolve 0.5 mol of 1-(2-bromoethyl)-3,5-dimethyl adamantane (II) in toluene, mix with 0.55 mol of sodium-bis(2-methoxy-ethoxy)dihydro aluminate, and heat to boiling for 3 hrs. After hydrolysis, separate the organic phase, dry with magnesium sulfate, and evaporate to dryness under vacuum. Purify the residue by vacuum distillation. (Yield: 86%).

D. Preparation of 1-Bromo-3,5-dimethyl-7-ethyl Adamantane (IV)

Mix 0.4 mol of 1,3-dimethyl-5-ethyl adamantane (III) with a ten times excess of bromine (4 mol). Heat slowly and stir for 4 hrs under reflux. Subsequently allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discolouration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 86%).

E. Preparation of 1-N-formyl-3,5-dimethyl-7-ethyl Adamantane (V)

Heat 0.2 mol of 1-bromine-3,5-dimethyl-7-ethyl adamantane (IV) with 150 ml of formamide at reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

F. Preparation of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (VI)

Mix 0.2 mol of 1-N-formyl-3,5-dimethyl-7-ethyl adamantane (V) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

EXAMPLE 9

Synthesis of 1-N-methylamino-3,5-dimethyl Adamantane (Test Compound No. 5)

Dissolve 0.1 mol of the appropriately substituted amino adamantane (1-amino-3,5-dimethyl adamantane) with 0.15 mol of chloromethyl formate and potassium carbonate in acetone and heat to reflux for 8 hrs. After cooling, filter the solution, remove the solvent and dry the residue. Mix the raw product (0.05 mol) with 0.1 mol of sodium-bis-(2-methoxy-ethoxy)-dihydro aluminate in toluene and heat at reflux for 3 hrs. After cooling, hydrolize with dilute HCl, dry the organic phase and evaporate to dryness. Purify the raw material by distillation.

EXAMPLE 10

Synthesis of 1-Amino-3-ethyl-5-phenyl Adamantane

A. Preparation of 1-Bromo-3-ethyl Adamantane (I)

Mix 0.034 mol of ethyl adamantane with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 hrs. Then allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Subsequently extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

B. Preparation of 1-Ethyl-3-phenyl Adamantane (II)

Heat 0.068 mol of iron(III) chloride in 20 ml of absolute benzene to boiling. Drop 0.0186 mol of 1-bromo-3-ethyl adamantane (I), dissolved in 30 ml of absolute benzene, into the solution. Then heat at reflux for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 80%).

C. Preparation of 1-Ethyl-3-hydroxy-5-phenyl Adamantane (III)

To a solution of 0.03 mol of chromiumtrioxide, in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-ethyl-3-phenyl adamantane (II) at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture into water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolize the residue with 20 ml of 2N NaOH and 50 ml of methanol. Remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629–35.

D. Preparation of 1-Bromo-3-ethyl-5-phenyl Adamantane (IV)

Stir 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (III) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and for 30 min at room temperature. Subsequently dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

E. Preparation of 1-N-formyl-3-ethyl-5-phenyl Adamantane (V)

Heat 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (IV) with 50 ml of formamide for 12 hrs at reflux. After cooling, pour the reaction mixture into water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness. (Yield: 80%).

F. Preparation of 1-Amino-3-ethyl-5-phenyl Adamantane Hydrochloride (VI)

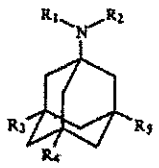
Heat 0.02 mol of 1-N-formyl-3-ethyl-5-phenyl adamantane (V) with 100 ml of 15% hydrochloric acid for 24 hrs at reflux. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

It is thus seen that certain adamantane derivatives, some of which are novel, have been provided for the prevention and treatment of cerebral ischemia, and that pharmaceutical compositions embodying such an adamantane derivative have been provided for use in the prevention and treatment of cerebral ischemia, the amount of the said adamantane derivative provided in either case being a cerebral ischemia-alleviating or preventive amount.

Various modifications and equivalents will be apparent to one skilled in the art and may be made in the compounds, compositions, methods, and procedures of the present invention without departing from the spirit or scope thereof, and it is therefore to be understood that the invention is to be limited only by the full scope which can be legally attributed to the appended claims.

We claim:

1. A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



(I)

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof.

2. A method according to claim 1, wherein R_1, R_2 and R_5 are hydrogen.

3. A method according to claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are methyl.

4. A method according to claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are ethyl.

5. A method according to claim 1, wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is ethyl, isopropyl, or cyclohexyl.

6. A method according to claim 1, wherein R_2 and R_5 are hydrogen.

7. A method according to claim 6, wherein R_3 and R_4 are methyl, R_2 and R_5 are hydrogen and R_1 is methyl or ethyl.

8. A method according to claim 1, wherein R_1 and R_2 are hydrogen.

9. A method according to claim 8, wherein R_1 and R_2 are hydrogen, R_3 is ethyl, and R_5 and R_4 are methyl.

10. A method according to claim 1 for the treatment of Alzheimer's disease.

11. A method of claim 1, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventive amount.

12. A method of claim 11, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

13. A method of claim 11, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,061,703 C1
APPLICATION NO. : 90/007176
DATED : November 7, 2006
INVENTOR(S) : Joachim Bormann et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, line 56: delete "wherein" and substitute --*wherein*--.

Claim 1, line 57: delete "R_4 *and*" and substitute --R_4, *and*--.

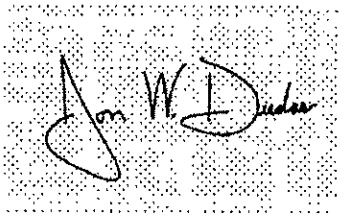
Claim 1, line 58: delete "*simultaneously;*" and substitute --*simultaneously,*--.

Claim 10, line 62: delete "disease *wherein*" and substitute --disease, *wherein*--.

Claim 18, line 64: delete "in" and substitute --is--.

Signed and Sealed this

Fifth Day of June, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT B

US005061703C1

(12) **EX PARTE REEXAMINATION CERTIFICATE** (5595th)
United States Patent
Bormann et al.

(10) **Number: US 5,061,703 C1**
(45) **Certificate Issued: Nov. 7, 2006**

(54) **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

(75) Inventors: **Joachim Bormann**, Frankfurt (DE); **Markus R. Gold**, Nauheim (DE); **Wolfgang Schatton**, Eschborn (DE)

(73) Assignee: **Merz Pharma GmbH & Co. KGaA**, Frankfurt am Main (DE)

Reexamination Request:
No. 90/007,176, Aug. 18, 2004

Reexamination Certificate for:
Patent No.: **5,061,703**
Issued: **Oct. 29, 1991**
Appl. No.: **07/508,109**
Filed: **Apr. 11, 1990**

(30) **Foreign Application Priority Data**

Apr. 14, 1989 (EP) 89106657

(51) **Int. Cl.**
A61K 31/55 (2006.01)
A61K 31/445 (2006.01)
A61K 31/41 (2006.01)

(52) **U.S. Cl.** **514/212.01**; 514/325; 514/359
(58) **Field of Classification Search** 514/212.01, 514/325, 359
See application file for complete search history.

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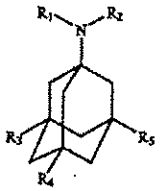
(Continued)

Primary Examiner—Kevin E. Weddington

(57) **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula

(I)



wherein

R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof, is disclosed.

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EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

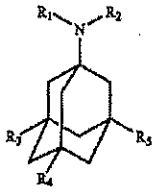
AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1 and 10 are determined to be patentable as amended.

Claims 2–9 and 11–13, dependent on an amended claim, are determined to be patentable.

New claims 14–19 are added and determined to be patentable.

1. A method for the prevention or treatment of cerebral ischemia comprising the step of *orally* administering, to a patient *diagnosed with Alzheimer's disease and* in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; *and*

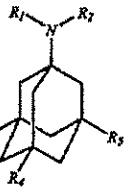
wherein

R_1, R_2, R_3, R_4 and R_5 do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

10. A method according to claim 1 for the treatment of Alzheimer's disease *wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.*

14. A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

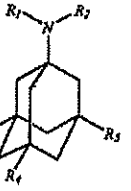
R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

15. The method of claim 14, wherein said adamantane derivative is memantine.

16. The method of claim 14, wherein said effective amount is from about 0.01 to 100 mg/kg.

17. A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

18. The method of claim 17, wherein said adamantane derivative in memantine.

19. The method of claim 17, wherein said effective amount is from about 0.01 to 100 mg/kg.

* * * * *

EXHIBIT 20

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

FILED
JAN 31 2008

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., MERZ PHARMA GMBH & CO. KGAA, and MERZ PHARMACEUTICALS GMBH,

Plaintiffs,

vs.

MYLAN PHARMACEUTICALS INC.,

Defendant.

Civil Action No. 1:08CV73

COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for their Complaint against Defendant Mylan Pharmaceuticals Inc. hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Mylan Pharmaceuticals Inc. ("Mylan") is a West Virginia corporation having a principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. Upon information and belief, Defendant Mylan manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

6. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. This Court has personal jurisdiction over Defendant Mylan by virtue of the fact that, *inter alia*, Mylan has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Labs, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court also has personal jurisdiction over Defendant Mylan for the

additional reason set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

9. This Court has personal jurisdiction over Defendant Mylan by virtue of the fact that, *inter alia*, Mylan is a West Virginia corporation.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

11. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

12. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

13. Forest is the exclusive distributor of Namenda® in the United States.

14. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

ACTS GIVING RISE TO THIS ACTION

Count I – Infringement Of The '703 Patent By Defendant Mylan

15. Upon information and belief, Defendant Mylan submitted ANDA No. 79-225 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). Mylan's ANDA No. 79-225 seeks FDA approval for the commercial manufacture, use

and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Mylan Generic Products"). Mylan's ANDA No. 79-225 specifically seeks FDA approval to market the Mylan Generic Products prior to the expiration of the '703 patent.

16. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Mylan alleged in ANDA No. 79-225 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Mylan Generic Products. Plaintiffs received written notification of ANDA No. 79-225 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 18, 2007.

17. Mylan's submission of ANDA No. 79-225 to the FDA, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Mylan commercially manufactures, uses, offers to sell, sells, or imports any of the Mylan Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

18. Mylan was aware of the '703 patent prior to filing ANDA No. 79-225.

19. Mylan's actions render this an exceptional case under 35 U.S.C. § 285.

20. Plaintiffs will be irreparably harmed by Mylan's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

21. Plaintiffs have sought to enjoin Defendant Mylan's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 25, 2008, Civil Action No. 1:08-CV-00052. Defendant Mylan is properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703

patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs understand that Defendant may nevertheless contest jurisdiction in that venue. Given the possible consequences if Defendant succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Defendant is unsuccessful in any such challenge, Plaintiffs will dismiss this action.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendant Mylan has infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendant's ANDA No. 79-225 identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendant, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: January 31, 2008

Respectfully submitted,

CRANSTON & EDWARDS, PLLC

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United States Patent [19]

Bormann et al.

[11] **Patent Number: 5,061,703**

[45] **Date of Patent: Oct. 29, 1991**

[54] **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

[75] Inventors: **Joachim Bormann**, Frankfurt; **Markus R. Gold**, Nauheim; **Wolfgang Schatton**, Eschborn, all of Fed. Rep. of Germany

[73] Assignee: **Merz + Co. GmbH & Co.**, Frankfurt am Main, Fed. Rep. of Germany

[21] Appl. No.: **508,109**

[22] Filed: **Apr. 11, 1990**

[30] **Foreign Application Priority Data**

Apr. 14, 1989 [EP] European Pat. Off. 89106657

[51] **Int. Cl.**[5] **A61K 31/13**; A61K 31/41; A61K 31/55; A61K 31/445

[52] **U.S. Cl.** **514/212**; 514/325; 514/359; 514/662

[58] **Field of Search** 514/212, 325, 359, 662

[56] **References Cited**

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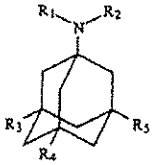
Primary Examiner—Stanley J. Friedman
Attorney, Agent, or Firm—Gordon W. Hueschen

[57] **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula



(I)

wherein

R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

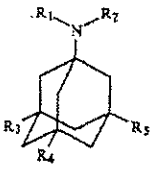
R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof, is disclosed.

13 Claims, No Drawings

ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA

The present invention relates to a method for the prevention or treatment of cerebral ischemia using an adamantane derivative of the following general formula



(I)

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic radical with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl; and

wherein

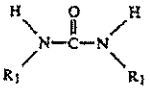
R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group, or a pharmaceutically-acceptable acid addition salt thereof. Herein branched or straight C_1–C_6 alkyl groups representatively include methyl, ethyl, iso- and n-propyl, n-, iso- and t-butyl, n-pentyl, n-hexyl, and the isomers thereof.

Certain 1-amino adamantanes of formula (I) are known. 1-amino-3,5-dimethyl adamantane, for example, is the subject matter of German patents 22 19 256 and 28 56 393.

Some 3,5-disubstituted 1-amino adamantanes of formula (I) are described in U.S. Pat. No. 4,122,193. 1-amino-3-ethyl adamantane is described in German Patent 22 32 735.

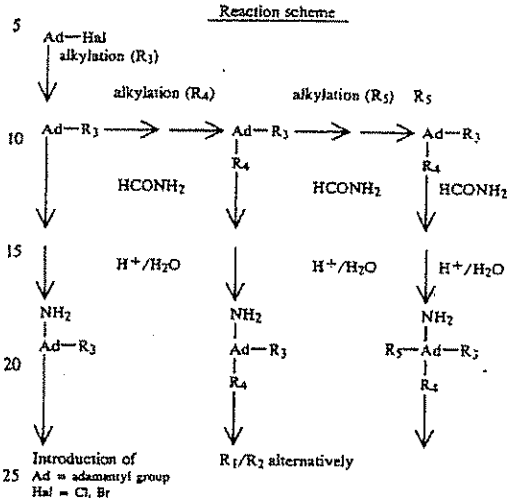
The compounds of formula (I) are generally prepared by alkylation of halogenated adamantanes, preferably bromo- or chloroadamantanes. The di- or tri-substituted adamantanes are obtained by additional halogenation and alkylation procedures. The amino group is introduced either by oxidation with chromiumtrioxide and bromination with HBr or bromination with bromine and reaction with formamide followed by hydrolysis. The amino function can be alkylated according to generally-accepted methods. Methylation can, for example, be effected by reaction with chloromethyl formate and subsequent reduction. The ethyl group can be introduced by reduction of the respective acetamide.

In accordance with U.S. Pat. No. 4,122,193 amination can also be effected by reaction of the respective 1-halogen-3,5- or -7-substituted adamantane with a urea derivative of the formula



wherein R_1 is hydrogen or alkyl.

The compounds according to formula (I) are prepared according to the following reaction scheme:



Alkylation of the halogenated adamantanes can be achieved by known methods, for example, through Friedel-Crafts reaction (introduction of phenyl group), or by reaction with vinylidene chloride, subsequent reduction and suitable Wittig reaction of the aldehydes and subsequent hydration, or by introduction of ethylene and subsequent alkylation with appropriate cuprates, or by introduction of ethylene and reduction of the halogen alkyl adamantanes, or by acylation with CO_2 and reduction of the carboxylic acid.

The compounds according to formula (I) known from the above-cited patents have so far been used for the treatment of parkinsonian and parkinsonoid diseases. Their mode of action is attributed to a dopaminergic influence on the CNS, either by an increased release of the transmitter substance dopamine or by an inhibition of its uptake. This compensates the imbalance of the dopamine/acetylcholine system.

In contrast to this type of disease, cerebral ischemia is characterized by a pathophysiological situation defined by an imbalance of neuronal stimulation mechanisms. In this context, the excessive inflow of calcium through NMDA receptor channels finally leads to the destruction of brain cells in specific brain areas (Rothmann & Olney, Trends Neurosci 10, 1989, pp. 299).

Therefore, in order to treat or eliminate this pathological situation, an antagonistic intervention is required with regard to the NMDA receptor channels (Kemp et al., Trends Pharmacol., Sci. 8, 1987. pp. 414).

Such intervention can, for example, be effected using substituted fluoro and hydroxy derivatives of dibenzo-[a,d]-cyclo-heptene-5,10-imine which are described in EP-A 0 264 183.

These heterocyclic, aromatic compounds are lipophilic and exhibit NMDA receptor channel-antagonistic and anticonvulsive properties. They are prepared by a relatively expensive method generating enantiomer mixtures which may be split into the individual optical antipodes.

The present invention is aimed at preparing and employing compounds which can be chemically generated

by simple methods, exhibiting an NMDA receptor channel-antagonistic and anticonvulsive action, for use in the prevention and treatment of cerebral ischemia.

This objective can be achieved according to the invention by using the 1-amino adamantanes of formula (I).

It has been found unexpectedly that the use of these compounds prevents an impairment or further impairment, i.e., degeneration and loss of nerve cells, after ischemia. Therefore, the adamantane derivatives of formula (I) are especially suited for the prevention and treatment of cerebral ischemia after apoplexy, open-heart surgery, cardiac standstill, subarachnoidal hemorrhage, transient cerebro-ischemic attacks, perinatal asphyxia, anoxia, hypoglycemia, apnoea and Alzheimer's disease. The amount employed is a cerebral ischemia-alleviating or preventive amount.

Examples of compounds prepared and used according to the invention are:

1-amino adamantane
1-amino-3-phenyl adamantane
1-amino-methyl-adamantane
1-amino-3,5-dimethyl adamantane (test compound no. 1)
1-amino-3-ethyl adamantane (test compound no. 2)
1-amino-3-isopropyl adamantane (test compound no. 3)
1-amino-3-n-butyl adamantane
1-amino-3,5-diethyl adamantane (test compound no. 4)
1-amino-3,5-diisopropyl adamantane
1-amino-3,5-di-n-butyl adamantane
1-amino-3-methyl-5-ethyl adamantane
1-N-methylamino-3,5-dimethyl adamantane (test compound no. 5)
1-N-ethylamino-3,5-dimethyl adamantane (test compound no. 6)
1-N-isopropyl-amino-3,5-dimethyl adamantane
1-N,N-dimethyl-amino-3.5-dimethyl adamantane
1-N-methyl-N-isopropyl-amino-3-methyl-5-ethyl adamantane
1-amino-3-butyl-5-phenyl adamantane
1-amino-3-pentyl adamantane
1-amino-3,5-dipentyl adamantane
1-amino-3-pentyl-5-hexyl adamantane
1-amino-3-pentyl-5-cyclohexyl adamantane
1-amino-3-pentyl-5-phenyl adamantane
1-amino-3-hexyl adamantane
1-amino-3,5-dihexyl adamantane
1-amino-3-hexyl-5-cyclohexyl adamantane
1-amino-3-hexyl-5-phenyl adamantane
1-amino-3-cyclohexyl adamantane (test compound no. 7)
1-amino-3,5-dicyclohexyl adamantane
1-amino-3-cyclohexyl-5-phenyl adamantane
1-amino-3,5-diphenyl adamantane
1-amino-3,5,7-trimethyl adamantane
1-amino-3,5-dimethyl-7-ethyl adamantane (test compound no. 8)
1-amino-3,5-diethyl-7-methyl adamantane
1-N-pyrrolidino and 1-N-piperidine derivatives,
1-amino-3-methyl-5-propyl adamantane
1-amino-3-methyl-5-butyl adamantane
1-amino-3-methyl-5-pentyl adamantane
1-amino-3-methyl-5-hexyl adamantane
1-amino-3-methyl-5-cyclohexyl adamantane
1-amino-3-methyl-5-phenyl adamantane
1-amino-3-ethyl-5-propyl adamantane
1-amino-3-ethyl-5-butyl adamantane
1-amino-3-ethyl-5-pentyl adamantane
1-amino-3-ethyl-5-hexyl adamantane
1-amino-3-ethyl-5-cyclohexyl adamantane
1-amino-3-ethyl-5-phenyl adamantane
1-amino-3-propyl-5-butyl adamantane
1-amino-3-propyl-5-pentyl adamantane
1-amino-3-propyl-5-hexyl adamantane
1-amino-3-propyl-5-cyclohexyl adamantane
1-amino-3-propyl-5-phenyl adamantane
1-amino-3-butyl-5-pentyl adamantane
1-amino-3-butyl-5-hexyl adamantane
1-amino-3-butyl-5-cyclohexyl adamantane

their N-methyl, N,N-dimethyl, N-ethyl, N-propyl derivatives and their acid addition compounds.

Preferred compounds of formula (I) are those wherein R_1 and R_2 are hydrogen such as, for example, 1-amino-3-ethyl-5,7-dimethyl adamantane, and compounds wherein R_1, R_2, R_4 and R_5 are hydrogen such as, for example, 1-amino-3-cyclohexyl adamantane and 1-amino-3-ethyl adamantane.

Additional preferred compounds are those wherein R_1, R_2 and R_5 are hydrogen such as, for example, 1-amino-3-methyl-5-propyl or 5-butyl adamantane, 1-amino-3-methyl-5-hexyl or cyclohexyl adamantane, or 1-amino-3-methyl-5-phenyl adamantane.

Especially preferred compounds are 1-amino-3,5-dimethyl adamantane, 1-amino-3,5-diethyl adamantane, i.e., compounds wherein R_1, R_2 and R_5 are hydrogen, and compounds wherein R_1 and R_5 are hydrogen, R_2 is methyl or ethyl, and R_3 and R_4 are methyl such as, for example, 1-N-methylamino-3,5-dimethyl adamantane and 1-N-ethylamino-3,5-dimethyl adamantane.

The adamantane derivatives of formula (I) may be applied as such or in the form of their pharmaceutically-acceptable acid addition salts including, for example, the hydrochlorides, hydrobromides, sulfates, acetates, succinates or tartrates, or their acid addition salts with fumaric, maleic, citric, or phosphoric acids.

The compounds of formula (I) are administered in suitable form in doses ranging from about 0.01 to 100 mg/kg. Appropriate presentation forms are, for example, combinations of the active substance with common pharmaceutical carriers and adjuvants in the form of tablets, coated tablets, and sterile solutions or suspensions for injection. Pharmaceutically-acceptable carriers are, for example, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, gum arabic, corn starch, or cellulose, combined with diluents such as water, polyethylene glycol, etc. Solid presentation forms are prepared according to common methods and may contain up to 50 mg of the active ingredient per unit.

The efficacy of the compounds of formula (I) is described in the following pharmacological tests.

A. Displacement of TCP Binding

Phencyclidine (PCP), a known NMDA antagonist, binds to the NMDA receptor-associated ionic channel and blocks ionic transport (Garthwaite & Garthwaite, Neurosci. Lett. 83, 1987, 241-246). Additionally, PCP has been shown to prevent the destruction of brain cells after cerebral ischemia in rats (Sauer et al., Neurosci. Lett. 91, 1988, 327-332).

The interaction between compounds of formula (I) and the PCP bond is studied in the following. In this test ^{3}H-TCP, a PCP analogue, is used.

A membrane preparation of rat cortex is incubated with ^{3}H-TCP which is an analogue of phencyclidine (PCP) (Quirion & Pert 1982, Eur. J. Pharmacol. 83:155).

The interaction with the TCP binding is assessed for test compound no. 1 (1-amino-3,5-dimethyl adamantane) in a competitive experiment. This test shows that compound no. 1 is very effective in displacing TCP from the bond. The IC_{50} value is 89 nM. The conclusion can be drawn that compound no. 1 binds to NMDA receptor channels at the same site as the NMDA antagonist PCP.

B. Blocking of NMDA Receptor Channels

In the following test it is shown that the compounds of formula (I) according to the invention are as effective as PCP in blocking the NMDA receptor channel.

In the patch-clamp experiment, the current flowing through NMDA-activated membrane channels of cultivated spinal marrow neurons (mouse) is measured (Hamill et al 1981, Pflügers Arch. 312: 85–100). After application of 20 μM NMDA, the current signal of the cell is integrated for 20 sec. and recorded as a control answer (A_c). During succeeding application of 20 μM NMDA and 6 μM of an adamantane derivative, the intensity of the substance effect can be determined as a relative change of the control answer ($A/A_c - A$ = test answer).

The results are summarized in the following Table 1:

TABLE 1

Compound no.	1-A/Ac	n
1	0.66 ± 0.05	14
2	0.44 ± 0.08	7
3	0.58 ± 0.07	7
4	0.50 ± 0.11	5
5	0.56 ± 0.07	7
6	0.38 ± 0.05	7
7	0.25 ± 0.04	11
8	0.50 ± 0.03	6
PCP	0.50 ± 0.04	7
MK-801	0.60 ± 0.05	22

The values are given as means ± SEM.

As can be seen from the results, the aminoadamantane derivatives of formula (I) are able to block the NMDA receptor channel as has been described for PCP (Bertolini et al., Neurosci. Lett. 84, 1988, 351–355) and for 5-methyl-10,11-dihydro-5H-dibenzo[a,d]cycloheptene-5,10-imine (MK-801) (EP-A 0 264 183).

C. Anticonvulsive Effect

4, 12, 36, 108 and 324 mg/kg of the test substance is administered to mice by the intraperitoneal route (5 animals per dose). The supermaximum electroshock test is applied forty (40) minutes after application of the substance to investigate the anti-convulsive potential of the substance. The protected animals are added up over all dosages (score; maximum=25 animals).

The results are given in the following Table 2.

TABLE 2

Compound no.	Anticonvulsive action (score)	Mean	ED_{50} (mg/kg)
1	18		
	16		
	16		
	15	16.3	16
2	15		
	14		
	12	13.7	30
4	16		
	16		
	11	14.3	24
5	17		
	17	17.0	13
Standards:			
PCP	19	19.0	9
MK-801	25	25.0	<1

The ED_{50} values were estimated according to Litchfield, J. T. and Wilcoxon, F., J. Pharmacol. Exp. Therap. 96, 99–113 (1949).

As can be seen from the above results, aminoadamantane derivatives of formula (I) exhibit a protective effect against electrically induced convulsions. They therefore have an anticonvulsive effect.

D. Correlation Between Channel-Blocking and Anticonvulsive Action

The correlation between the action of the tested adamantane derivatives 1–8 at the NMDA receptor channel (in vitro) and the anticonvulsive effect (in vivo) has been tested. For this purpose an xy diagram of both test parameters is plotted. It shows that there is a correlation between the blocking of the NMDA receptor channel and the anticonvulsive action of the adamantanes of formula (I).

E. Protection Against Cerebral Ischemia

Both carotid arteries are occluded in rats for 10 minutes. At the same time the blood pressure is reduced to 60–80 mg Hg by withdrawal of blood (Smith et al. 1984, Acta Neurol. Scand. 69: 385, 401). The ischemia is terminated by opening the carotids and reinfusion of the withdrawn blood. After seven days the brains of the test animals are histologically examined for cellular changes in the CA1–CA4 region of the hippocampus, and the percentage of destroyed neurons is determined. The action of test compound No. 1 is determined after a single administration of 5 mg/kg and 20 mg/kg one (1) hour prior to the ischemia.

The results are summarized in the following Table 3:

TABLE 3

Area	Control	Test compound no. 1: 5 mg/kg (n = 5)	Test compound no. 1: 20 mg/kg (n = 6)
CA1	80.2 ± 1.5	83.0 ± 2.2	53.1 ± 6.1**
CA3	3.6 ± 1.1	7.3 ± 1.8	2.7 ± 1.0
CA4	1.4 ± 0.4	3.7 ± 1.7	0.6 ± 0.3

The values are given in percent of damaged neurons ± SEM.
Significance of the mean difference: **p < 0.01 (U test)

The results show that the reduction of the post-ischemic neuronal brain damage in the CA1 region of the rat hippocampus is statistically significant after the pre-ischemic application of 20 mg/kg of test compound no. 1. Physiological parameters (e.g. blood pressure, body temperature) are not affected by the treatment. Moreover, the results show that the compounds according to formula (I) exhibit a neuroprotective action in cerebral ischemia.

Essentially the same result is attained by employing the compounds of the other Examples, especially those designated test compounds 2–8.

F. Protection Against NMDA-Induced Mortality

It is well known that, subsequent to cerebral ischemia, glutamate and aspartate levels increase massively in the brain. These excitatory aminoacids overstimulate

the NMDA-subtype of the glutamate receptor thus leading to delayed neuronal death. A similar pathophysiological situation is obtained when mice are administered intraperitoneally with 200 mg/kg NMDA. This high dose will eventually cause 100% mortality in the animals (Leander et al. 1984, Brain Res. 448; 115–120). We have found that the adamantane derivatives of the present invention are protective against the NMDA-induced mortality.

Compound No.	Dose mg/kg	Protected Animals
1	50	8/8
	25	6/8
	10	3/8
3	50	6/8
	25	4/8
4	50	7/8
	25	5/8
5	25	5/8

In the control animals, to which no adamantane was administered, the mortality was eight (8) animals out of eight (8).

G. Displacement of [^{3}H] MK-801 Binding in Human Brain Tissue

MK-801 binds to the ion channel associated with the NMDA receptor, as well as TCP does. This binding site is thought to mediate the neuroprotective effects of non-competitive NMDA-antagonists.

We have investigated whether the adamantane derivatives of the present invention are active at the MK-801 binding site. Tissue from frontal cortex was taken from patients at autopsy and homogenates were prepared. Inhibition of specific [^{3}H] MK-801 binding (3 nM) by the test compounds was determined (see e.g. Kornhuber et al. 1989, Eur. J. Pharmacol. 166: 589–590).

The test compounds were highly potent in displacing MK-801 binding, thus indicating a specific interaction with the NMDA receptor channel and predicting neuroprotective properties.

Compound No.	Ki nM
1	536
3	598
4	189
5	1607

wherein K_i is the inhibition constant and nM is nanomoles per liter. Mean values from triplicate experiments are given ± S.E.M.

The inhibition constant Ki is approximately equal to the concentration of the adamantane in nM required to displace 50% of the MK-801 specifically bound to the receptor. In this regard, memantine (Compound No. 1) was found to be the most potent compound subjected to this test, when compared with thirteen (13) other clinically-used and centrally-acting drugs, as reported in the foregoing publication.

The invention is further described by the following illustrative examples, which are not to be construed as limiting:

EXAMPLE 1

Injectable Solution

For preparing a 0.5% solution, dissolve 0.5% active ingredient and 0.8% sodium chloride (DAB 9) in doubly distilled water. Filter the solution through an antimicrobial filter, fill into 2-ml ampoules and sterilize for 20 minutes at 120° C. in an autoclave.

EXAMPLE 2

Solution

Dissolve 1% of active agent in demineralized water. Filter the solution before filling.

EXAMPLE 3

Tablets

1 tablet contains:	
Active ingredient	10.0 mg
Lactose	67.5 mg
Microcrystalline cellulose	18.0 mg
Talc	4.5 mg
	100.0 mg

The substances are mixed and the mixture compressed into 100-mg tablets in a direct tableting procedure without granulation.

EXAMPLE 4

Coated Tablets

Prepare 6-mm tablet cores of 100 mg as described under "Tablets". Coat the tablets in a sugar-coating process by coating the core with a sugar suspension first, followed by staining with a colored syrup and polishing.

The tablet coating consists of:

Sugar	65.0 mg
Talc	39.0 mg
Calcium carbonate	13.0 mg
Gum arabic	6.5 mg
Corn starch	3.7 mg
Shellac	1.1 mg
Polyethylene glycol 6000	0.2 mg
Magnesia usta	1.3 mg
Dye	0.2 mg
	130.0 mg

Total tablet weight: 230 mg

EXAMPLE 5

For preparing a 0.01% infusion solution, dissolve 0.01% of active ingredient and 5% levulose in doubly-distilled water. Filter the solution through an antimicrobial filter, fill into 500-ml infusion bottles, and sterilize.

The example provides 50 mg of active substance per single dose.

EXAMPLE 6

Synthesis of 1-Amino-3-isopropyl Adamantane Hydrochloride (Test Compound No. 3)

A. Preparation of Adamantane Methyl Carboxylate (I)

Stir 1.0 mol of adamantane carboxylic acid in 600 ml of methanol. Under ice cooling, drop 1.53 mol of acetyl chloride into the solution within 1 h. Remove the ice bath, and allow the reaction mixture to reach room temperature. Subsequently, heat for 3 hrs under reflux. Evaporate the reaction mixture to dryness under vacuum and distill. (Yield: 97%).

B. Preparation of Isopropyl Adamantane (II)

Introduce 0.5 mol of magnesium chips into 50 ml of absolute ether, and drop 0.5 mol of methyl iodide into the solution under moisture-free conditions until the ether boils. Subsequently, heat in a water bath until the magnesium has completely dissolved. Into this solution at room temperature drop 0.2 mol of adamantane methyl carboxylate in absolute ether. Then heat to reflux for 3 hours. After cooling, hydrolize with ice and mix with ammonium chloride solution until the precipitate has dissolved. Separate the ether phase, wash the aqueous phase with 2 portions of ether, and wash the combined organic phases with sodium bicarbonate solution. Then dry and evaporate to dryness under vacuum. (Yield: 93%).

C. Preparation of Isopropene Adamantane (III)

Stir 0.25 mol of isopropyl adamantane (II) in 500 ml acetic anhydride for 12 hours at 160° C. Subsequently, pour the reaction mixture onto 1 liter of ice water and extract with ether. Dry the combined organic phases with magnesium sulfate, filter, and evaporate to dryness under vacuum. Distill the residue under vacuum. (Yield: 66%).

D. Preparation of Isopropyl Adamantane (IV)

Dissolve 0.074 mol of adamantyl isopropene (III) in 100 ml of absolute ethanol. Add 4 g of palladium (5% on activated carbon) and hydrate under stirring for 24 hrs at room temperature. Subsequently, filter off the catalyst, and remove the solvent under vacuum. (Yield: 91%).

E. Preparation of 1-Bromo-3-isopropyl Adamantane (V)

Mix 0.034 mol of isopropyl adamantane (IV) with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 h. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until the aqueous solution has discolored. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

F. Preparation of 1-N-formyl-3-isopropyl Adamantane (VI)

Heat 0.028 mol of 1-bromo-3-isopropyl adamantane (V) with 40 ml of formamide to reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

G. Preparation of 1-Amino-3-isopropyl Adamantane Hydrochloride

Mix 0.023 mol of 1-N-formyl-3-isopropyl adamantane (VI) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

EXAMPLE 7

Synthesis of 1-Amino-3-cyclohexyl Adamantane Hydrochloride (Test Compound No. 7)

A. Preparation of 1-Phenyl Adamantane (I)

Heat 0.068 mol of iron(III) chloride to boiling in 20 ml of absolute benzene. Drop 0.0186 mol of 1-bromoadamantane, dissolved in 30 ml of absolute benzene, to the solution. Then heat to boiling for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract the aqueous phase with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 80%).

B. Preparation of 1-Hydroxy-3-phenyl Adamantane (II)

To a solution of 0.03 mol chromiumtrioxide in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-phenyl adamantane at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture onto water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolize the residue with 20 ml of 2N NaOH and 50 ml of methanol. Subsequently, remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629–35.

C. Preparation of 1-Bromo-3-phenyl Adamantane (III)

Stir 0.03 mol of 3-phenyl adamantanol (II) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and 30 min at room temperature. Subsequently, dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

D. Preparation of 1-N-formyl-3-phenyl Adamantane (IV)

Heat 0.03 mol of 1-bromo-3-phenyl adamantane (III) with 50 ml of formamide for 12 hrs to reflux. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 80%).

E. Preparation of 1-Amino-3-phenyl Adamantane Hydrochloride (V)

Heat 0.02 mol of 1-N-formyl-3-phenyl adamantane (IV) with 100 ml of 15% hydrochloric acid at reflux for 24 hours. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

F. Preparation of 1-Amino-3-cyclohexyl Adamantane (VI)

Dissolve 0.011 mol of 1-amino-3-phenyl adamantane (V) in 150 ml glacial acetic acid, mix with 0.3 g of platinum oxide (1% on activated carbon) and hydrate in a

Parr apparatus at 35° C. at a hydrogen pressure of 3 bar. Subsequently, remove the catalyst by filtration and evaporate the filtrate to dryness. Take up the residue in methanol and precipitate the product with ether. Suck off and dry. (Yield: 70%).

EXAMPLE 8

Synthesis of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (Test Compound No. 8)

A. Preparation of 1-Bromo-3,5-dimethyl Adamantane (I)

Mix 0.5 mol of 1,3-dimethyl adamantane with a ten times excess of bromine (5 mol). Slowly heat and stir for 4 hrs under reflux. Subsequently, allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

B. Preparation of 1-(2-Bromoethyl)-3,5-dimethyl Adamantane (II)

Mix 1.4 mol of 1-bromo-3,5-dimethyl adamantane (I) in hexane with 0.6 mol of aluminum bromide at −75° C. Subsequently, pass ethylene through the solution for 20–30 minutes, stir for 5 min., and pour the reaction mixture onto ice water. Extract with ether, dry the organic phase and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 48%).

C. Preparation of 1,3-Dimethyl-5-ethyl Adamantane (III)

Dissolve 0.5 mol of 1-(2-bromoethyl)-3,5-dimethyl adamantane (II) in toluene, mix with 0.55 mol of sodium-bis(2-methoxy-ethoxy)dihydro aluminate, and heat to boiling for 3 hrs. After hydrolysis, separate the organic phase, dry with magnesium sulfate, and evaporate to dryness under vacuum. Purify the residue by vacuum distillation. (Yield: 86%).

D. Preparation of 1-Bromo-3,5-dimethyl-7-ethyl Adamantane (IV)

Mix 0.4 mol of 1,3-dimethyl-5-ethyl adamantane (III) with a ten times excess of bromine (4 mol). Heat slowly and stir for 4 hrs under reflux. Subsequently allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discolouration of the aqueous solution. Then extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 86%).

E. Preparation of 1-N-formyl-3,5-dimethyl-7-ethyl Adamantane (V)

Heat 0.2 mol of 1-bromine-3,5-dimethyl-7-ethyl adamantane (IV) with 150 ml of formamide at reflux for 12 hrs. After cooling, pour the reaction mixture onto water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness under vacuum. (Yield: 82%).

F. Preparation of 1-Amino-3,5-dimethyl-7-ethyl Adamantane Hydrochloride (VI)

Mix 0.2 mol of 1-N-formyl-3,5-dimethyl-7-ethyl adamantane (V) with 100 ml of 15% hydrochloric acid and heat to boiling for 24 hrs. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 57%).

EXAMPLE 9

Synthesis of 1-N-methylamino-3,5-dimethyl Adamantane (Test Compound No. 5)

Dissolve 0.1 mol of the appropriately substituted amino adamantane (1-amino-3,5-dimethyl adamantane) with 0.15 mol of chloromethyl formate and potassium carbonate in acetone and heat to reflux for 8 hrs. After cooling, filter the solution, remove the solvent and dry the residue. Mix the raw product (0.05 mol) with 0.1 mol of sodium-bis-(2-methoxy-ethoxy)-dihydro aluminate in toluene and heat at reflux for 3 hrs. After cooling, hydrolize with dilute HCl, dry the organic phase and evaporate to dryness. Purify the raw material by distillation.

EXAMPLE 10

Synthesis of 1-Amino-3-ethyl-5-phenyl Adamantane

A. Preparation of 1-Bromo-3-ethyl Adamantane (I)

Mix 0.034 mol of ethyl adamantane with a ten times excess of bromine (0.33 mol). Heat slowly and stir under reflux for 4 hrs. Then allow to cool and pour onto ice water. Decompose the excess bromine with sodium sulfite until discoloration of the aqueous solution. Subsequently extract with ether, wash the combined organic phases with sodium bicarbonate solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 83%).

B. Preparation of 1-Ethyl-3-phenyl Adamantane (II)

Heat 0.068 mol of iron(III) chloride in 20 ml of absolute benzene to boiling. Drop 0.0186 mol of 1-bromo-3-ethyl adamantane (I), dissolved in 30 ml of absolute benzene, into the solution. Then heat at reflux for 3 hrs. After cooling, pour the reaction mixture onto ice/hydrochloric acid, separate the organic phase, and extract with two portions of benzene. Wash the combined organic phases with water, dry with calcium chloride, filter and evaporate to dryness. Recrystallize the residue from methanol. (Yield: 80%).

C. Preparation of 1-Ethyl-3-hydroxy-5-phenyl Adamantane (III)

To a solution of 0.03 mol of chromiumtrioxide, in 20 ml glacial acetic acid and 20 ml acetic anhydride, add 0.0095 mol of 1-ethyl-3-phenyl adamantane (II) at 0° C. and stir for 24 hours at 4° C. Pour the reaction mixture into water and extract with three portions of pentane. Wash the organic phase with saturated sodium chloride solution, dry over magnesium sulfate, filter and evaporate to dryness under vacuum. Hydrolize the residue with 20 ml of 2N NaOH and 50 ml of methanol. Remove the methanol under vacuum and dilute the residue with water. Then extract with three portions of ether. Dry the organic phase, filter and evaporate to dryness under vacuum. Recrystallize the residue from cyclohexane. (Yield: 50%).

Ref.: H. Stetter, M. Schwarz, A. Hirschhorn, Chem. Ber. (1959), 92, 1629–35.

D. Preparation of 1-Bromo-3-ethyl-5-phenyl Adamantane (IV)

Stir 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (III) with 100 ml of 40% HBr in glacial acetic acid for 20 min at 60° C. and for 30 min at room temperature. Subsequently dilute the reaction mixture with water and extract with ether. Wash the combined organic extracts with sodium chloride solution, dry with magnesium sulfate, filter and evaporate to dryness under vacuum. Recrystallize the residue from methanol. (Yield: 68%).

Ref.: W. Fischer, C. A. Grog, Helvetica Chim. Acta (1976), 59, 1953.

E. Preparation of 1-N-formyl-3-ethyl-5-phenyl Adamantane (V)

Heat 0.03 mol of 1-ethyl-3-hydroxy-5-phenyl adamantane (IV) with 50 ml of formamide for 12 hrs at reflux. After cooling, pour the reaction mixture into water and extract with dichloromethane. Dry the combined organic phases with magnesium sulfate, filter and evaporate to dryness. (Yield: 80%).

F. Preparation of 1-Amino-3-ethyl-5-phenyl Adamantane Hydrochloride (VI)

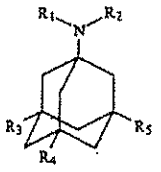
Heat 0.02 mol of 1-N-formyl-3-ethyl-5-phenyl adamantane (V) with 100 ml of 15% hydrochloric acid for 24 hrs at reflux. After cooling, filter the precipitate and recrystallize from isopropanol. (Yield: 60%).

It is thus seen that certain adamantane derivatives, some of which are novel, have been provided for the prevention and treatment of cerebral ischemia, and that pharmaceutical compositions embodying such an adamantane derivative have been provided for use in the prevention and treatment of cerebral ischemia, the amount of the said adamantane derivative provided in either case being a cerebral ischemia-alleviating or preventive amount.

Various modifications and equivalents will be apparent to one skilled in the art and may be made in the compounds, compositions, methods, and procedures of the present invention without departing from the spirit or scope thereof, and it is therefore to be understood that the invention is to be limited only by the full scope which can be legally attributed to the appended claims.

We claim:

1. A method for the prevention or treatment of cerebral ischemia comprising the step of administering, to a patient in need thereof, an effective amount of an adamantane derivative of the general formula



(I)

wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof.

2. A method according to claim 1, wherein R_1, R_2 and R_5 are hydrogen.

3. A method according to claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are methyl.

4. A method according to claim 2, wherein R_1, R_2 and R_5 are hydrogen, and R_3 and R_4 are ethyl.

5. A method according to claim 1, wherein R_1, R_2, R_4 and R_5 are hydrogen, and R_3 is ethyl, isopropyl, or cyclohexyl.

6. A method according to claim 1, wherein R_2 and R_5 are hydrogen.

7. A method according to claim 6, wherein R_3 and R_4 are methyl, R_2 and R_5 are hydrogen and R_1 is methyl or ethyl.

8. A method according to claim 1, wherein R_1 and R_2 are hydrogen.

9. A method according to claim 8, wherein R_1 and R_2 are hydrogen, R_3 is ethyl, and R_5 and R_4 are methyl.

10. A method according to claim 1 for the treatment of Alzheimer's disease.

11. A method of claim 1, wherein the adamantane derivative is administered in an effective cerebral ischemia-alleviating or preventive amount.

12. A method of claim 11, wherein the adamantane derivative is administered in the form of a composition containing the same together with a pharmaceutically-acceptable carrier or diluent.

13. A method of claim 11, wherein the adamantane derivative is administered in an amount effective to prevent degeneration and loss of nerve cells after ischemia.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,061,703 C1
APPLICATION NO. : 90/007176
DATED : November 7, 2006
INVENTOR(S) : Joachim Bormann et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Claim 1, line 56: delete "wherein" and substitute –*wherein*–.

Claim 1, line 57: delete "R_4 *and*" and substitute –R_4, *and*–.

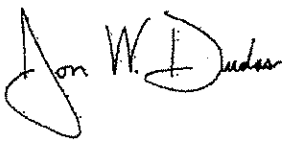
Claim 1, line 58: delete "*simultaneously;*" and substitute –*simultaneously,*–.

Claim 10, line 62: delete "disease *wherein*" and substitute –disease, *wherein*–.

Claim 18, line 64: delete "in" and substitute –is–.

Signed and Sealed this

Fifth Day of June, 2007



JON W. DUDAS
Director of the United States Patent and Trademark Office

US005061703C1

(12) EX PARTE REEXAMINATION CERTIFICATE (5595th)

United States Patent

Bormann et al.

(10) Number: US 5,061,703 C1

(45) Certificate Issued: Nov. 7, 2006

(54) **ADAMANTANE DERIVATIVES IN THE PREVENTION AND TREATMENT OF CEREBRAL ISCHEMIA**

(75) Inventors: **Joachim Bormann**, Frankfurt (DE); **Markus R. Gold**, Nauheim (DE); **Wolfgang Schatton**, Eschborn (DE)

(73) Assignee: **Merz Pharma GmbH & Co. KGaA**, Frankfurt am Main (DE)

Reexamination Request:
No. 90/007,176, Aug. 18, 2004

Reexamination Certificate for:

Patent No.:	5,061,703
Issued:	Oct. 29, 1991
Appl. No.:	07/508,109
Filed:	Apr. 11, 1990

(30) **Foreign Application Priority Data**

Apr. 14, 1989 (EP) 89106637

(51) **Int. Cl.**

A61K 31/55	(2006.01)
A61K 31/445	(2006.01)
A61K 31/41	(2006.01)

(52) **U.S. Cl.** **514/212.01**; 514/325; 514/359

(58) **Field of Classification Search** 514/212.01, 514/325, 359

See application file for complete search history.

(56) **References Cited**

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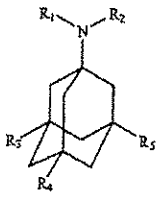
(Continued)

Primary Examiner—Kevin E. Weddington

(57) **ABSTRACT**

A method for the prevention and treatment of cerebral ischemia using an adamantane derivative of the formula

(I)



wherein

R_1 and R_2 are identical or different, representing hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1-C_6 alkyl group,

or a pharmaceutically-acceptable salt thereof, is disclosed.

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EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

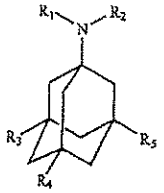
AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims 1 and 10 are determined to be patentable as amended.

Claims 2–9 and 11–13, dependent on an amended claim, are determined to be patentable.

New claims 14–19 are added and determined to be patentable.

1. A method for the prevention or treatment of cerebral ischemia comprising the step of *orally* administering, to a patient *diagnosed with Alzheimer's disease and* in need thereof, an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; *and*

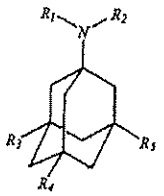
wherein

R_1, R_2, R_3, R_4 and R_5 do not all represent hydrogen simultaneously;

or a pharmaceutically-acceptable salt thereof.

10. A method according to claim 1 for the treatment of Alzheimer's disease *wherein said adamantane derivative is memantine and said effective amount is from about 0.01 to 100 mg/kg.*

14. A method for the treatment of cerebral ischemia comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

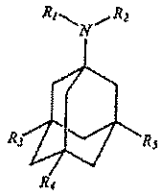
R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

15. The method of claim 14, wherein said adamantane derivative is memantine.

16. The method of claim 14, wherein said effective amount is from about 0.01 to 100 mg/kg.

17. A method for the treatment of an imbalance of neuronal stimulation after Alzheimer's disease, comprising orally administering to a patient diagnosed with Alzheimer's disease and in need of such treatment an effective amount of an adamantane derivative of the general formula



wherein

R_1 and R_2 are identical or different and represent hydrogen or a straight or branched alkyl group of 1 to 6 C atoms or, in conjunction with N, a heterocyclic group with 5 or 6 ring C atoms;

wherein

R_3 and R_4 are identical or different, being selected from hydrogen, a straight or branched alkyl group of 1 to 6 C atoms, a cycloalkyl group with 5 or 6 C atoms, and phenyl;

wherein

R_5 is hydrogen or a straight or branched C_1–C_6 alkyl group; and

wherein

R_1, R_2, R_3, R_4, and R_5 do not all represent hydrogen simultaneously,

or a pharmaceutically-acceptable salt thereof.

18. The method of claim 17, wherein said adamantane derivative in memantine.

19. The method of claim 17, wherein said effective amount is from about 0.01 to 100 mg/kg.

* * * * *

EXHIBIT 21

FILED
JAMES BONINI
CLERK

2008 FEB -4 P 1:50

U.S. DISTRICT COURT
SOUTHERN DIST. OHIO
EAST. DIV. COLUMBUS

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF OHIO

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., MERZ PHARMA GMBH & CO. KGAA, and MERZ PHARMACEUTICALS GMBH,

Plaintiffs,

vs.

KENDLE INTERNATIONAL INC.,

Defendant.

Civil Action No. 1:08cv78

COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for their Complaint against Defendant Kendle International Inc. hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Kendle International Inc. ("Kendle") is an Ohio corporation having a principal place of business at 441 Vine Street, Suite 1200, Cincinnati, Ohio 45202. Upon information and belief, Defendant Kendle conducts business throughout the United States, including in this judicial district.

NATURE OF THE ACTION

6. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq*.

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. This Court has personal jurisdiction over Defendant Kendle by virtue of the fact that, *inter alia*, Kendle has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Labs, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court has personal jurisdiction over Kendle for the additional reason set

forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

9. This Court has personal jurisdiction over Defendant Kendle by virtue of the fact that, *inter alia*, Kendle is an Ohio corporation.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

11. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

12. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

13. Forest is the exclusive distributor of Namenda® in the United States.

14. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

ACTS GIVING RISE TO THIS ACTION

Count I – Infringement Of The '703 Patent By Defendant Kendle

15. Upon information and belief, Defendant Kendle, on behalf of its principal Sun India Pharmaceutical Industries Limited ("Sun India") (a/k/a Sun Pharmaceutical Industries Limited), submitted ANDA No. 90-058 to the FDA under § 505(j) of the Federal Food, Drug and

Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Sun Generic Products"). ANDA No. 90-058 specifically seeks FDA approval to market the Sun Generic Products prior to the expiration of the '703 patent.

16. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Kendle alleged in ANDA No. 90-058, on behalf of its principal Sun India, that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Sun Generic Products. Plaintiffs received written notification of ANDA No. 90-058 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 20, 2007.

17. Kendle's submission of ANDA No. 90-058 to the FDA, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Kendle commercially manufactures, uses, offers to sell, sells, or imports any of the Sun Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

18. Kendle was aware of the '703 patent prior to filing ANDA No. 90-058.

19. Kendle's actions render this an exceptional case under 35 U.S.C. § 285.

20. Plaintiffs will be irreparably harmed by Kendle's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

21. Plaintiffs have sought to enjoin Defendant Kendle's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 25, 2008, Civil Action No. 1:08-CV-00052.

Defendant Kendle is properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs understand that Defendant may nevertheless contest jurisdiction in that venue. Given the possible consequences if Defendant succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Defendant is unsuccessful in any such challenge, Plaintiffs will dismiss this action.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendant Kendle has infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA No. 90-058 identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendant, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: February 4, 2008

Respectfully submitted,

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EXHIBIT 22

FILED
FEBRUARY 4, 2008
MICHAEL W. DOBBINS
CLERK, U.S. DISTRICT COURT

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF ILLINOIS

08 C 749

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., MERZ PHARMA GMBH & CO. KGAA, and MERZ PHARMACEUTICALS GMBH,

Plaintiffs,

vs.

SUN INDIA PHARMACEUTICAL INDUSTRIES LIMITED (a/k/a/ SUN PHARMACEUTICAL INDUSTRIES LIMITED),

Defendant.

Civil Action No. JUDGE CASTILLO
MAGISTRATE JUDGE VALDEZ

COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for their Complaint against Defendant Sun India Pharmaceutical Industries Limited (a/k/a Sun Pharmaceutical Industries Limited) hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Sun India Pharmaceutical Industries Limited ("Sun India") (a/k/a Sun Pharmaceutical Industries Limited) is an Indian corporation having a principal place of business at Acme Plaza, Andheri Kurla Road, Andheri (East), Mumbai, Maharashtra 400 059, India. Upon information and belief, Defendant Sun India manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

6. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. This Court has personal jurisdiction over Defendant Sun India by virtue of the fact that, *inter alia*, Sun India has committed, or aided, abetted, contributed to and/or

participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Labs, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court has personal jurisdiction over Sun India for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

9. This Court has personal jurisdiction over Defendant Sun India by virtue of, *inter alia*: (1) its systematic and continuous contacts with Illinois; and (2) the fact that Sun India, in its notice to Plaintiffs pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, has consented to jurisdiction in Illinois by its designation of James F. Hurst, Esq., an attorney practicing in this District, as an agent in the United States "authorized to accept service of process on behalf of SUN INDIA."

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

11. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

12. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

13. Forest is the exclusive distributor of Namenda® in the United States.

14. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

ACTS GIVING RISE TO THIS ACTION

Count I – Infringement Of The '703 Patent By Defendant Sun India

15. Upon information and belief, Defendant Sun India, through its agent Kendle International Inc. ("Kendle"), submitted ANDA No. 90-058 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Sun Generic Products"). ANDA No. 90-058 specifically seeks FDA approval to market the Sun Generic Products prior to the expiration of the '703 patent.

16. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Sun India alleged in ANDA No. 90-058 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Sun Generic Products. Plaintiffs received written notification of ANDA No. 90-058 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 20, 2007.

17. Sun India's submission of ANDA No. 90-058 to the FDA, through its agent Kendle, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Sun India commercially manufactures, uses, offers to sell, sells, or imports any of the Sun Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

18. Sun India was aware of the '703 patent prior to filing ANDA No. 90-058.

19. Sun India's actions render this an exceptional case under 35 U.S.C. § 285.

20. Plaintiffs will be irreparably harmed by Sun India's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

21. Plaintiffs have sought to enjoin Defendant Sun India's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 25, 2008, Civil Action No. 1:08-CV-00052. Defendant Sun India is properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs understand that Defendant may nevertheless contest jurisdiction in that venue. Given the possible consequences if Defendant succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Defendant is unsuccessful in any such challenge, Plaintiffs will dismiss this action.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendant Sun India has infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendant's ANDA No. 90-058 identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendant, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: February 4, 2008

Respectfully submitted,

KIRKLAND & ELLIS LLP

/s/ William E. Devitt

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Of Counsel:

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EXHIBIT 23

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., MERZ PHARMA GMBH & CO. KGAA, and MERZ PHARMACEUTICALS GMBH, Plaintiffs, vs. LUPIN PHARMACEUTICALS, INC. and LUPIN LTD., Defendants.	Civil Action No. _____

COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for their Complaint against Defendants Lupin Pharmaceuticals, Inc. and Lupin Ltd. (collectively "Defendants") hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Lupin Pharmaceuticals, Inc. ("Lupin Pharma") is a Virginia corporation, and the wholly-owned subsidiary and agent of Defendant Lupin Ltd., having a principal place of business at Harborplace Tower, 111 S. Calvert Street, 21st Floor, Baltimore, Maryland 21202. Upon information and belief, Defendant Lupin Pharma manufactures and/or distributes numerous generic drugs for sale and use throughout the United States, including in this judicial district.

6. Upon information and belief, Defendant Lupin Ltd. ("Lupin") is an Indian corporation having a principal place of business at Laxmi Towers, B Wing, Bandra Kurla Complex, Bandra (East), Mumbai, Maharashtra 400 051, India. Upon information and belief, Defendant Lupin, itself and through its wholly-owned subsidiary and agent Defendant Lupin Pharma, manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

7. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

JURISDICTION AND VENUE

8. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Labs, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

10. This Court has personal jurisdiction over Defendant Lupin Pharma by virtue of the fact that, *inter alia*, Lupin Pharma's principal place of business is located in Maryland.

11. This Court has personal jurisdiction over Defendant Lupin by virtue of, *inter alia*: (1) its presence in Maryland through its subsidiary and agent Lupin Pharma; and (2) its systematic and continuous contacts with Maryland, including through its subsidiary and agent Lupin Pharma.

12. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

13. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United

States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

14. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

15. Forest is the exclusive distributor of Namenda® in the United States.

16. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

ACTS GIVING RISE TO THIS ACTION

Count I – Infringement Of The '703 Patent By Defendants Lupin And Lupin Pharma

17. Upon information and belief, Defendant Lupin, through its subsidiary and agent Lupin Pharma, submitted ANDA No. 90-051 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Lupin Generic Products"). ANDA No. 90-051 specifically seeks FDA approval to market the Lupin Generic Products prior to the expiration of the '703 patent.

18. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Lupin alleged in ANDA No. 90-051 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Lupin Generic Products. Plaintiffs received written notification of ANDA No. 90-051 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 14, 2007.

19. Lupin's submission of ANDA No. 90-051 to the FDA, through its subsidiary and agent Lupin Pharma, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin commercially manufacturers, uses, offers to sell, sells, or imports any of the Lupin Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

20. Lupin Pharma is jointly and severally liable for any infringement of the '703 patent. Upon information and belief, Lupin Pharma participated in, contributed to, aided, abetted and/or induced Lupin's submission of ANDA No. 90-051 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

21. Lupin Pharma's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 90-051 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Pharma commercially manufactures, uses, offers to sell, sells, or imports any of the Lupin Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

22. Lupin and Lupin Pharma were aware of the '703 patent prior to filing ANDA No. 90-051.

23. Lupin's and Lupin Pharma's actions render this an exceptional case under 35 U.S.C. § 285.

24. Plaintiffs will be irreparably harmed by Lupin's and Lupin Pharma's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

25. Plaintiffs have sought to enjoin Defendant Lupin's and Defendant Lupin Pharma's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 10, 2008, Civil Action No. 08-021 GMS. Defendants Lupin and Lupin Pharma are properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs understand that Defendants may nevertheless contest jurisdiction in that venue. Given the possible consequences if Defendants succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Defendants are unsuccessful in any such challenge, Plaintiffs will dismiss this action.

26. Plaintiffs have also sought to enjoin Defendant Lupin's and Defendant Lupin Pharma's infringing activities in an action filed concurrently today in the District of Columbia. That action was necessary because, as of the present date, it cannot be determined with certainly which of Lupin or Lupin Pharma was the filer of ANDA No. 90-051. Upon information and belief, Plaintiffs understand that Defendants may contest jurisdiction over Defendant Lupin in this venue. Given the possible consequences if Defendants succeeded with such unjustified action, Plaintiffs had no choice but to file a concurrent Complaint in the District of Columbia.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendants Lupin and Lupin Pharma have infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendants' ANDA No. 90-051 identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendants Lupin and Lupin Pharma, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: January 28, 2008

Respectfully submitted,

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EXHIBIT 24

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

FOREST LABORATORIES, INC.
909 Third Avenue, New York, New York 10022,

FOREST LABORATORIES HOLDINGS, LTD.
Milner House, 18 Parliament Street, Hamilton JM11, Bermuda,

MERZ PHARMA GMBH & CO. KGAA
Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany, and

MERZ PHARMACEUTICALS GMBH
Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany,

Plaintiffs,

vs.

LUPIN PHARMACEUTICALS, INC.
Harborplace Tower, 111 S. Calvert Street, 21st Floor, Baltimore, Maryland 21202, and

LUPIN LTD.
Laxmi Towers, B Wing, Bandra Kurla Complex, Bandra (East), Mumbai, Maharashtra 400 051, India

Defendants.

Civil Action No. _____

Case: 1:08-cv-00167
Assigned To : Kollar-Kotelly, Colleen
Assign. Date : 1/28/2008
Description: General Civil

COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for

1

their Complaint against Defendants Lupin Pharmaceuticals, Inc. and Lupin Ltd. (collectively "Defendants") hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Lupin Pharmaceuticals, Inc. ("Lupin Pharma") is a Virginia corporation, and the wholly-owned subsidiary and agent of Defendant Lupin Ltd., having a principal place of business at Harborplace Tower, 111 S. Calvert Street, 21st Floor, Baltimore, Maryland 21202. Upon information and belief, Defendant Lupin Pharma manufactures and/or distributes numerous generic drugs for sale and use throughout the United States, including in this judicial district.

6. Upon information and belief, Defendant Lupin Ltd. ("Lupin") is an Indian corporation having a principal place of business at Laxmi Towers, B Wing, Bandra Kurla

Complex, Bandra (East), Mumbai, Maharashtra 400 051, India. Upon information and belief, Defendant Lupin, itself and through its wholly-owned subsidiary and agent Defendant Lupin Pharma, manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

7. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq.*

JURISDICTION AND VENUE

8. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9. This Court has personal jurisdiction over each of the Defendants by virtue of the fact that, *inter alia*, each Defendant has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Labs, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court has personal jurisdiction over each of the Defendants for the additional reasons set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

10. This Court has personal jurisdiction over Defendant Lupin Pharma by virtue of, *inter alia*: (1) its systematic and continuous contacts with the District of Columbia; and (2) the fact that its parent company, Lupin, in its notice to Plaintiffs pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, has consented to jurisdiction in the District of Columbia by its designation of Mark Attar, Esq., an attorney

practicing in this District, as "an agent in the United States authorized to accept service of process" on its behalf.

11. This Court has personal jurisdiction over Defendant Lupin by virtue of, *inter alia*: (1) its systematic and continuous contacts with the District of Columbia, including through its subsidiary and agent Lupin Pharma; and (2) Lupin, in its notice to Plaintiffs pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, has consented to jurisdiction in the District of Columbia by its designation of Mark Attar, Esq., an attorney practicing in this District, as "an agent in the United States authorized to accept service of process" on its behalf.

12. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

13. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

14. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

15. Forest is the exclusive distributor of Namenda® in the United States.

16. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

ACTS GIVING RISE TO THIS ACTION

Count I – Infringement Of The '703 Patent By Defendants Lupin And Lupin Pharma

17. Upon information and belief, Defendant Lupin, through its subsidiary and agent Lupin Pharma, submitted ANDA No. 90-051 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). That ANDA seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams and 10 milligrams of memantine hydrochloride ("the Lupin Generic Products"). ANDA No. 90-051 specifically seeks FDA approval to market the Lupin Generic Products prior to the expiration of the '703 patent.

18. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Lupin alleged in ANDA No. 90-051 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Lupin Generic Products. Plaintiffs received written notification of ANDA No. 90-051 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 14, 2007.

19. Lupin's submission of ANDA No. 90-051 to the FDA, through its subsidiary and agent Lupin Pharma, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin commercially manufacturers, uses, offers to sell, sells, or imports any of the Lupin Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

20. Lupin Pharma is jointly and severally liable for any infringement of the '703 patent. Upon information and belief, Lupin Pharma participated in, contributed to, aided, abetted and/or induced Lupin's submission of ANDA No. 90-051 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA.

21. Lupin Pharma's participation in, contribution to, aiding, abetting and/or inducement of the submission of ANDA No. 90-051 and its § 505(j)(2)(A)(vii)(IV) allegations to the FDA constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Lupin Pharma commercially manufactures, uses, offers to sell, sells, or imports any of the Lupin Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

22. Lupin and Lupin Pharma were aware of the '703 patent prior to filing ANDA No. 90-051.

23. Lupin's and Lupin Pharma's actions render this an exceptional case under 35 U.S.C. § 285.

24. Plaintiffs will be irreparably harmed by Lupin's and Lupin Pharma's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

25. Plaintiffs have sought to enjoin Defendant Lupin's and Defendant Lupin Pharma's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 10, 2008, Civil Action No. 08-021 GMS. Defendants Lupin and Lupin Pharma are properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs understand that Defendants may nevertheless contest jurisdiction in that venue. Given the possible consequences if Defendants succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Defendants are unsuccessful in any such challenge, Plaintiffs will dismiss this action.

26. Plaintiffs have also sought to enjoin Defendant Lupin's and Defendant Lupin Pharma's infringing activities in an action filed concurrently today in the District of Maryland. That action was necessary because, as of the present date, it cannot be determined with certainly which of Lupin or Lupin Pharma was the filer of ANDA No. 90-051. Upon information and belief, Plaintiffs understand that Defendants may contest jurisdiction over Defendant Lupin Pharma in this venue. Given the possible consequences if Defendants succeeded with such unjustified action, Plaintiffs had no choice but to file a concurrent Complaint in the District of Maryland.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendants Lupin and Lupin Pharma have infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendants' ANDA No. 90-051 identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendants Lupin and Lupin Pharma, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: January 28, 2008

Respectfully submitted,

Gregory A. Castanias (D.C. Bar No. 441129)
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EXHIBIT 25

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MINNESOTA

FOREST LABORATORIES, INC., FOREST LABORATORIES HOLDINGS, LTD., MERZ PHARMA GMBH & CO. KGAA, and MERZ PHARMACEUTICALS GMBH,

Plaintiffs,

vs.

UPSHER-SMITH LABORATORIES, INC.,

Defendant.

Civil Action No. 08CV253 ADM/JSM

COMPLAINT

Plaintiffs Forest Laboratories, Inc., Forest Laboratories Holdings, Ltd., Merz Pharma GmbH & Co. KGaA, and Merz Pharmaceuticals GmbH (collectively "Plaintiffs") for their Complaint against Defendant Upsher-Smith Laboratories, Inc. hereby allege as follows:

PARTIES

1. Plaintiff Forest Laboratories, Inc. ("Forest Labs") is a Delaware corporation having a principal place of business at 909 Third Avenue, New York, New York 10022.

2. Plaintiff Forest Laboratories Holdings, Ltd. is an Irish corporation having a principal place of business at Milner House, 18 Parliament Street, Hamilton JM11, Bermuda (referred to herein, together with Forest Laboratories, Inc., as "Forest").

3. Plaintiff Merz Pharma GmbH & Co. KGaA is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany.

SCANNED
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U.S. DISTRICT COURT MPLS

4. Plaintiff Merz Pharmaceuticals GmbH is a German corporation having a principal place of business at Eckenheimer Landstraße 100, D-60318 Frankfurt am Main, Germany (referred to herein, together with Merz Pharma GmbH & Co. KGaA, as "Merz").

5. Upon information and belief, Defendant Upsher-Smith Laboratories, Inc. ("Upsher-Smith") is a Minnesota corporation having a principal place of business at 6701 Evenstad Drive, Maple Grove, Minnesota 55369. Upon information and belief, Defendant Upsher-Smith manufactures numerous generic drugs for sale and use throughout the United States, including in this judicial district.

NATURE OF THE ACTION

6. This is a civil action for infringement of United States Patent No. 5,061,703 ("the '703 patent") (Exhibit A). This action is based upon the Patent Laws of the United States, 35 U.S.C. § 1 *et seq*.

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

8. This Court has personal jurisdiction over Defendant Upsher-Smith by virtue of the fact that, *inter alia*, Upsher-Smith has committed, or aided, abetted, contributed to and/or participated in the commission of, the tortious act of patent infringement that has led to foreseeable harm and injury to Plaintiffs, including a corporation, Plaintiff Forest Laboratories, which manufactures numerous drugs for sale and use throughout the United States, including in this judicial district. This Court has personal jurisdiction over Defendant Upsher-Smith for the additional reason set forth below and for other reasons that will be presented to the Court if such jurisdiction is challenged.

9. This Court has personal jurisdiction over Defendant Upsher-Smith by virtue of the fact that, *inter alia*, Upsher-Smith is a Minnesota corporation.

10. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

THE PATENT-IN-SUIT

11. On October 29, 1991, the '703 patent, titled "Adamantane Derivatives in the Prevention and Treatment of Cerebral Ischemia," was duly and legally issued by the United States Patent and Trademark Office ("PTO"). Merz has been, and continues to be, the sole assignee of the '703 patent since its issuance.

12. Forest is the exclusive licensee of the '703 patent in the United States. Forest holds New Drug Application ("NDA") No. 21-487 for Namenda® brand memantine hydrochloride tablets. The '703 patent is listed in the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") for Namenda®.

13. Forest is the exclusive distributor of Namenda® in the United States.

14. On August 18, 2004, Merz submitted a request to the PTO for reexamination of the '703 patent. The PTO issued a reexamination certificate (Exhibit B) for the '703 patent on November 7, 2006.

ACTS GIVING RISE TO THIS ACTION

Count I – Infringement Of The '703 Patent By Defendant Upsher-Smith

15. Upon information and belief, Defendant Upsher-Smith submitted ANDA No. 90-043 to the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(j)). Upsher-Smith's ANDA No. 90-043 seeks FDA approval for the commercial manufacture, use and sale of generic tablet products containing 5 milligrams, 10 milligrams, 15 milligrams, and 20 milligrams of memantine hydrochloride ("the Upsher-Smith Generic Products"). Upsher-

Smith's ANDA No. 90-043 specifically seeks FDA approval to market the Upsher-Smith Generic Products prior to the expiration of the '703 patent.

16. Pursuant to § 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act, Upsher-Smith alleged in ANDA No. 90-043 that the claims of the '703 patent are invalid, unenforceable and/or not infringed by the commercial manufacture, use or sale of the Upsher-Smith Generic Products. Plaintiffs received written notification of ANDA No. 90-043 and its § 505(j)(2)(A)(vii)(IV) allegation on or about December 14, 2007.

17. Upsher-Smith's submission of ANDA No. 90-043 to the FDA, including its § 505(j)(2)(A)(vii)(IV) allegations, constitutes infringement of the '703 patent under 35 U.S.C. § 271(e)(2)(A). Moreover, if Upsher-Smith commercially manufactures, uses, offers to sell, sells, or imports any of the Upsher-Smith Generic Products, or induces or contributes to any such conduct, it would further infringe the '703 patent under 35 U.S.C. § 271(a), (b) and/or (c).

18. Upsher-Smith was aware of the '703 patent prior to filing ANDA No. 90-043.

19. Upsher-Smith's actions render this an exceptional case under 35 U.S.C. § 285.

20. Plaintiffs will be irreparably harmed by Upsher-Smith's infringing activities unless those activities are enjoined by this Court. Plaintiffs do not have an adequate remedy at law.

21. Plaintiffs have sought to enjoin Defendant Upsher-Smith's infringing activities as part of an action to enjoin acts of infringement of the '703 patent by numerous defendants filed by Plaintiffs in the District of Delaware on January 10, 2008, Civil Action No. 08-021 GMS. Defendant Upsher-Smith is properly subject to personal jurisdiction in the District of Delaware and judicial economy would be promoted if all of Plaintiffs' claims for infringement of the '703 patent are addressed in the District of Delaware. Upon information and belief, Plaintiffs

understand that Defendant may nevertheless contest jurisdiction in that venue. Given the possible consequences if Defendant succeeded with such unjustified action, Plaintiffs had no choice but to file this Complaint. In the event that Defendant is unsuccessful in any such challenge, Plaintiffs will dismiss this action.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment as follows:

A. That Defendant Upsher-Smith has infringed the '703 patent;

B. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of Defendant's ANDA identified in this Complaint shall not be earlier than the expiration date of the '703 patent, including any extensions;

C. That Defendant, its officers, agents, servants and employees, and those persons in active concert or participation with any of them, be preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale, selling, or importing any of the proposed generic versions of Plaintiffs' Namenda® brand product identified in this Complaint and any other product that infringes or induces or contributes to the infringement of the '703 patent, prior to the expiration of the '703 patent, including any extensions;

D. That this case is exceptional under 35 U.S.C. § 285;

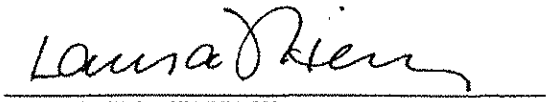
E. That Plaintiffs be awarded the attorney fees, costs and expenses that they incur prosecuting this action; and

F. That Plaintiffs be awarded such other and further relief as this Court deems just and proper.

Dated: January 28, 2008

Respectfully submitted,

GRAY PLANT MOOTY



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January 28, 2008

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CLERK U.S. DISTRICT COURT
MINNEAPOLIS, MN

BY MESSENGER

Clerk of Court
U.S. Courthouse
300 South Fourth Street
Suite 202
Minneapolis, MN 55415

RE: ***Forest Laboratories, Inc., et al. v. Upsher-Smith Laboratories, Inc.***

Dear Clerk of Court:

I enclose for filing the originals and one copy of the following materials:

1. Summons;
2. Complaint;
3. Civil Cover Sheet;
4. Corporate Disclosure Statement of Forest Laboratories, Inc.;
5. Corporate Disclosure Statement of Forest Laboratories Holdings, Ltd.;
6. Corporate Disclosure Statement of Merz Pharma GmbH & Co. KGaA;
7. Corporate Disclosure Statement of Merz Pharmaceuticals GmbH; and
8. Filing fee check in the amount of $350.00.

Please issue the Summons and return to the undersigned via messenger, along with a date-stamped copy of the Complaint. Thank you in advance and do not hesitate to contact me if you have any questions or comments.

Very truly yours,

GRAY, PLANT, MOOTY,
MOOTY & BENNETT, P.A.

By Laura J. Hein
Laura J. Hein

LJH/ps
Enclosures